MAGIC IN A BOTTLE

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TORONTO

TO

Chauncey D. Leake

WHO MEASURES DOSES BUT
NEVER FRIENDSHIP, AND WHO
STARTED THE WHOLE THING

Acknowledgment

THE chief characters in this book are real men and women (although in some cases their conversations are necessarily imaginary) and all incidents herein are based on fact. Sincere appreciation is due all those who dug into their files and their memories to make possible the telling of these tales—William Dock, Herbert M. Evans, Robley D. Evans, Howard W. Florey, C. Frederic Fluhmann, Joseph G. Hamilton, Carl Koller, John H. Lawrence, William G. Lennox, Samuel Lepkovsky, E. K. Marshall, Jr., Nina Simmonds, and many others, and particularly the book's three godparents, Maurice Tainter, Chauncey D. Leake, and Margaret Silverman.

Foreword

THERE is all the difference in the world between the pills that were given to my great-great-grandfather and the pills that my children take today.

Great-great-grandfather swallowed a concoction of colchicum and fennel water and Bavarian tar, well mixed, with sassafras and oil of wintergreen and powdered opium and rue. That brew didn't do him much good, for he died in spite of it—or maybe because of it.

Today my son and my daughter take carefully measured amounts of 2-methyl-5-(4-methyl-5-*beta*-hydroxyethyl-thiazolium chloride) methyl-6-aminopyrimidine-hydrochloride, and they stay strong and healthy.

Is this just a difference in the components of the pills? Don't you believe it! It is a difference in thinking, in philosophy, in fighting against death—and it has revolutionized the art of medicine.

The old eighteenth-century doctors tried to save great-great-grandfather by throwing a handful of assorted medical "pebbles" to drive out some nebulous devil or "humour." They couldn't throw pebbles accurately, and so great-great-grandfather died when he was quite young. But the twentieth-century doctor protects my children with a single magic bullet, aimed straight at the exact devil that tries to harm them. And that's why all the statisticians will bet their shirts that my children and yours will live longer than their parents or their grandparents or their great-great-grandparents before them.

You can look at the names of these new pills—long complex chemical names, with methyls and hydroxies and pyrimidines,

and say it's all much too complicated. Well, it is complicated. But automobiles are complicated, too, and so are television transmitters and jet engines and synthetic silk stockings and all the other triumphs of our day. They're just as complex as they can be—and yet we use them because they give the results we want.

In the very same way, we use these pure drugs against disease or let the doctor use them on us; for to most of us it's the result that counts and not the complexities behind it.

But there must be something else behind the drugs, something besides results and chemical formulas and dizzying pharmacodynamic philosophizing. There must be men. Behind every bottle in the bathroom cabinet and behind every jar on the druggist's shelf, there must be men, human beings who fought and hunted and made human mistakes, who were sometimes greedy and proud, who rose to peaks of glorious brilliance. There must be men who actually went out and *worked* to find aspirin, veronal, vitamin B_1, and penicillin.

This book is their story, the story of the men behind the chief drugs in modern medicine. They were wonderful people.

SAN FRANCISCO
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Contents

FOREWORD ix

I. *The Conquest of Pain* 1
SERTUERNER AND MORPHINE

II. *The Amazing Alkaloids* 26
PELLETIER AND QUININE

III. *Housewife's Recipe* 60
WITHERING AND DIGITALIS

IV. *Blessing from Hell* 89
KOLLER AND COCAINE

V. *Kill the Germs!* 116
LISTER TO EHRLICH TO 205

VI. *The Fever-Fighters* 145
KOLBE TO ASPIRIN

VII. *Synthetic Lullaby* 164
FISCHER, VON MERING, AND THE BARBITALS

VIII. *Food Against Death* 182
EIJKMAN AND THE VITAMINS

IX. *Magnificent Trifles* 212
BROWN-SÉQUARD AND THE HORMONES

X. *The Red Assassin* 242
DOMAGK AND THE SULFA-DRUGS

XI. *Miraculous Accident* 269

FLEMING, FLOREY, AND PENICILLIN

XII. *The Devil-Slayers* 299

LOCOCK TO LENNOX, AND THE DRUGS AGAINST EPILEPSY

XIII. *Atomic Medicine* 328

BECQUEREL, THE CURIES, AND THE ATOM-SMASHERS

BIBLIOGRAPHY 364

INDEX 379

CHAPTER I

The Conquest of Pain

SERTUERNER AND MORPHINE

ONCE upon a time there lived a remarkable man named Robinson Crusoe.

There are those who claim that Robinson is still alive and will live forever—which is as it should be—but unfortunately he is quite dead, and so is his man Friday, and so is the captain who came to their rescue.

Actually, Robinson Crusoe was Alexander Selkirk, a hot-blooded young Scotsman who was rescued from lonely Juan Fernández Island early in 1709, and his rescuer was Captain Thomas Dover of the privateer *Duke*. Just as Robinson still lives in the world of legend and adventure, so Captain Dover lives in the world of science. It is Dover who starts this story of drugs.

In 1710 Selkirk and Captain Dover arrived in London with a shipload of treasure, a captured Spanish frigate of twenty-one guns, and certain additional wealth. Selkirk possessed his own story, which he promptly sold to Daniel Defoe. Dover capitalized on an astounding quantity of sheer, unmitigated gall; he announced he would be a physician.

"Splendid!" they told him. "And with whom will you study?"

"Study? Good Lord," he laughed, "I am already forty years old. I have no time for study. I shall just start curing patients."

Did anyone intend to do anything about it?

The distinguished College of Physicians, England's "organized medicine," certainly had such intentions and went marching into battle. But Captain Dover told them to run along and mind their

own business, and with commendable tact and reserve he dismissed them as a clan of most prejudiced gentlemen.

He declared war on the London apothecaries and accused them of making outrageously extortionate charges.

He became a seven-years' wonder and the profane darling of London society.

Then he invented a new medicine, a combination of opium and ipecac which sold by the barrelful under the name of Dover's Powder and still sells today. It was good, too; in small doses it cured all kinds of aches and pains. But Dover had no patience with small doses.

"If one grain is good," he said, "then two grains must be better."

So he gave his powder in doses of sixty or even one hundred grains (the modern doctor shudders at giving more than five!), and apothecaries advised patients to take the medicine only after making their wills.

By the time Dover's murderous prescription came into existence, opium, or dried poppy juice, had already been used for sixty centuries. It had been passed from the ancient Sumerians to the Egyptians and then to the Arabs. It had been picked up by the Venetians, the Portuguese, the Dutch, and the English, who finally forced it on the Chinese—a bit of strategy which the white men conveniently forgot later on.

For sixty centuries—an exceedingly long history for even a good drug—opium made possible and bearable the practice of medicine. It was the only drug that could kill pain and produce sleep with reasonable safety. But Captain Dover ended all that.

His doses were so overpowering, and his results so terrible, that doctors began to tremble in their boots at the least mention of opium. On the other hand, some opium appeared on the market so highly adulterated that it was as useless as dishwater.

Consequently, half a century after Dover's ingenious invention, a new breed of doctors appeared—young men who had been taught by their saddened professors that it was really better to

had not the least suspicion of what was happening to him. He repaired the apothecary scales—and learned how to weigh drugs. He reorganized the stock room—and memorized the long list of Latin names which camouflaged each drug. He learned how to wait on customers, to fill prescriptions, even to gossip pleasantly, to discuss theology with the village priest, and to curse with the burgomaster at that mad Napoleon over in France.

"What I can't understand," Frederick told his mother, "is how Herr Cramer ever got along without me."

No, Frederick had not figured on Cramer.

When the old apothecary had palmed off all the easy tasks on the boy, he devised a whole array of new jobs.

"Tomorrow, Frederick, I wish you could give me some help. I can't find out how to measure the amount of benzoic acid in fennel-water. Do you think you might work out some way to . . ."

"Certainly, Herr Cramer, I know just where to look. I'll do it this afternoon!"

After fennel water, borax had to be studied, as did nutgalls, animal charcoal, tannins, and the amount of saltpeter in sugar beets. Cramer picked these ideas out of the air like flies. It was the beginning of research, and Cramer had never done research before in his life. He wasn't actually doing it now—he was merely suggesting and letting Sertuerner do the work; then one morning Sertuerner himself suggested the next topic for investigation.

"Herr Cramer!" he greeted his master. "Did you hear about little Anna Wollenberg?"

"Frau Wollenberg's youngest? No, what happened?"

"Well, it was terrible, Herr Cramer. She was playing next to the stove, and her mother spilled a kettle of scalding water on her. It burned her face, her shoulders, and her arms. She screamed all last night and—well, it was awful!"

"Good Heavens!" said Cramer. "Didn't they call the doctor?"

"Oh, yes, Dr. Schmidt was there, and he gave her opium, a lot of opium, but it didn't work."

"It didn't work?"

"No, Herr Cramer. Dr. Schmidt says we made a mistake; that we gave him something else instead of opium."

Cramer's jaw dropped. "But that is impossible," he exclaimed. "I remember filling that last prescription for him myself. I remember taking it from the opium bottle. There *can't* be any mistake. Wait, Frederick, here comes Dr. Schmidt. Let me talk to him."

The doctor, red-eyed, angry, dead tired, walked into the shop.

"Good morning, Dr. Schmidt."

"Well, Cramer?"

"Well, I—Frederick just told me about the little girl. It's frightful. But I can assure you, Dr. Schmidt, there was no mistake. I filled it myself, from . . ."

"I know," Schmidt interrupted. "I didn't mean to accuse you. Last night I was just excited. You didn't do anything. But there was a mistake."

"What do you mean?"

"That opium. There's something funny there, Cramer, and I want to know what it is!"

"But I . . ."

"Listen. Last year you sold me opium for Herr Weiss. It made him more miserable than his gout. Three months ago you gave me some that nearly killed the Bergmann's servant, kept her unconscious for three days. And now this new batch I used on little Anna—drachms of it, ounces of it, you hear that? It was worthless as water. Cramer, I don't blame you, but somebody is making a mistake. Your opium is no good. I can't count on it!"

"I know why."

The two men turned to young Sertuerner, standing in the doorway, and Dr. Schmidt waved his hand bitterly. "Go away, boy. This is none of your business."

Later, when the doctor had gone, Cramer called his assistant. "Frederick, what did you mean a little while ago, eh? You said you knew something. What do you know?"

Sertuerner pulled the big opium bottle from the shelf, took out

the cork, and rolled a few fragments of the powdery gum on the table. "What is this, Herr Cramer?"

"Why, that's opium, of course!"

"Is it pure?"

"Certainly it is. It's the purest you can—oh! Oh, I see what you mean. No Frederick, it's not pure. It's a mixture. It contains a lot of oily things and salts, and maybe some acids, and perhaps many other parts."

"Do you think all those things are necessary? Do you think all those salts and oils and all the rest of 'em—do they have to be in opium to make it put people to sleep and stop their pain?"

"Well, Frederick, I'm sure I don't know. What do you think?"

"I think this, Herr Cramer. I think that one of these things in opium is what really works. See? And all the others are just useless. Now, if one batch of opium is too weak, that means there isn't enough of that *something*. And if it's too strong, then there's too much!"

Cramer nodded slowly.

"All right," Sertuerner continued. "Now, if we could extract that *something* and get rid of all the rest, then we would have what's important. It would be *pure,* Herr Cramer. We could weigh it accurately. It would always give just the right effect—just enough to stop the pain and never enough to be dangerous."

Cramer carefully swept up the bits of opium and dropped them, one after another, into the bottle. He dusted his hands and gazed at his apprentice.

"Listen to me, Frederick," he said finally. "Maybe I know what you're talking about. Maybe I don't. But you talk about a *something* in this opium—how do you know there is such a thing? Have you ever seen it? Have you ever touched it or tasted it? No. Nobody has. Has anybody ever extracted such an active thing from any drug? No, Frederick, nobody ever has."

"But, Herr Cramer, don't you think we could *look* for it?"

"No, I do not. Listen to me—*if* there is such a thing, we don't

know how to get it out. *If* it exists, it might take years of work to find it. And furthermore, my boy, my shop is all right for little experiments on charcoal and fennel water, but it is not to be used for experiments on opium. It's too dangerous and—and anyhow, I don't like it!" But as he put the bottle back on the shelf, he added, "However, Herr Sertuerner, if you choose to disregard my advice, you will find some extra opium on the top shelf of the storeroom. And you will please to confine your experiments to the hours between six and ten at night. . . ."

Cramer had predicted all too wisely. This opium business was a lot trickier than fennel water or charcoal. Years went by and Serteurner had found nothing. He took time to take and pass his pharmacist's examination and then went back to opium, but still there was nothing.

Night after night the young assistant, refusing to leave Cramer's employ, kept on with his heretical tests and played one wild hunch after another. Carefully planned attacks, worked out in infinite detail, bored him. He waited for a bright idea and then tested it.

Finally he came to the idea that worked. He dissolved a batch of opium in acid—a simple process, for he'd learned to do that months before—and then, for no reason in the world, he wondered what might happen if he neutralized this acid solution with alkaline ammonia.

He took a bottle of ammonia and carefully emptied it into the clear opium solution. The solution became hot—that was the ammonia reacting with the acid—and then it cooled. And then suddenly, as if a magician had gone into action, the transparent solution became dull and cloudy. Where once there had been a water-clear liquid, he saw a batch of crystals appear out of nowhere and slowly sink to the bottom of the flask.

"Opium is brown and these crystals are gray," he whispered. "This stuff is no opium. . . ."

Maybe—maybe this was the *something* that stopped pain.

Well, it wasn't.

"Never mind," counseled Cramer, "it may be important anyhow.

I think you should write a scientific report and send it to somebody. Perhaps to Professor Trommsdorff."

Sertuerner, now twenty, broke into print. He sat down and wrote a simple letter to the great Trommsdorff at the University of Erfurt. He described his new compound and finished with an apology: "I cannot determine whether this is a new or an already known compound, for business keeps me from further investigation. However, it deserves consideration because of the great role played by opium in medicine. . . ."

Trommsdorff stormed. "Of all the juvenile prattle! Does this Sertuerner consider his child's play to be scientific research?" But against his better judgment, he printed the report in his journal.

But how could Trommsdorff know—how could Serteurner or Cramer—that mixed among those gray crystals were also the white crystals of another substance, a substance so strange and wonderful that it would some day revolutionize the very practice of medicine?

It took months of slow, laborious testing before Sertuerner began to suspect that the second compound was also there and still more months to dig it out, but eventually he got it. And this made no sense at all—this second compound was an alkali!

It wasn't the alkaline ammonia that Sertuerner had used in his extraction method. It was an alkali apparently present in the crude opium. And, according to all the textbooks, plants and plant derivatives didn't contain any alkalies. All right, so the textbooks were wrong.

Furthermore this new compound, this alkali, produced sleep. Sertuerner proved this with bungling, awkward experiments on animals—on rats and mice from Cramer's cellar and on cats and dogs which unwisely strolled through the town square after dark. This work had to be done very quietly, for Cramer would not look kindly upon animal tests for a new, untried substance.

So Sertuerner worked late at night, when he knew he would be undisturbed, seeking the effects of his new crystals on living tissue. He took these crystals—white, lustrous, odorless, and bitter as sin —and dissolved them in alcohol with a little sugar-syrup to hide

the taste. Then he forced them, somehow or other, down the gullet of his first dog.

"Lord," he wondered, "how much should I give? Five grains?"

He gave five grains, and this first animal slept for two days and died. Too big a dose. He cut it in half and tried again. The next dog died in a coma. Still too much.

Again and again he tried, each time using smaller doses, until after weeks of agonizing testing he reached the proper amount. Now he could put his animals to sleep with at least a faint hope that they would wake again. This, he knew, was the *something* he'd been hunting, the vital essence of opium.

He wrote his second report and shipped it off to Trommsdorff: "I have been fortunate enough to find in opium still another substance which has been unknown until now. . . . It is neither earth, gluten nor resin, nor the compound I found last year, but an entirely individual one. This substance is the specific narcotic element of opium . . . the *Principium somniferum.*"

Here, by the gods of science, was a masterpiece! A young pharmacist, only twenty-three, had found the mystery of opium. More than that, he had found a method, a chemical key, which would unlock the pure active principles in other crude drugs. And he had done all this without training, without help, without the gleaming laboratories, the complicated apparatus, and the purebred animals which modern scientists procure with a few lines on a requisition blank. But Trommsdorff, the great editor, was not impressed.

Trommsdorff published the report all right, but at the end he appended an editorial note: "The experiments contain many interesting suggestions, but we can by no means consider that the work on opium is concluded. We hope that these new claims will be investigated further and many obscure features elucidated. *There have been so many works on opium. . . .*"

Sertuerner was furious. "Look what that man said about me!" he shouted at Cramer. "Here, read what he said—that—that idiot, that old nincompoop! What does he know about opium? I'll—I'll write him—I'll tell him—to his face, mind you! I'll show him. . . ."

"Wait a minute!" Cramer roared back. "Frederick, you must not go on like that! Now, listen to me—just cool down for a few days, and everything will be all right. Now, won't you do that for me?"

"No!" Sertuerner became petulant. "No, everything won't be all right. I'll never touch opium again. Never!"

Frederick Sertuerner left Cramer's shop and in 1806 moved to the near-by town of Einbeck in South Hanover. Thanks to Cramer's aid, he found an opening there as assistant in the city pharmacy. He resolved to do nothing but dispense drugs and to do that with very bad grace. The world had treated him poorly. But soon he grew interested in caustic soda and caustic potash and then in galvanism, and he was back doing research.

He did good research, too, but now he ran into new difficulties—he couldn't get his reports published. "It's a conspiracy," he claimed, "not just against me, but against all Germans. We can't get recognition, even in our own country!"

And that was perfectly true. German science was still unborn; there were no great laboratories, no great scientific teachers. German scientists were mocked in their own land while the honors went to the French, the English, and the Swedes.

In great disgust Sertuerner dropped all his drug studies and turned to making bigger and better cannons, stronger and more powerful explosives to hurl against the hated Napoleon, and for that he received high honors. The honors disgusted him even more. By accident he returned to the study of opium.

One night he awoke with a raging toothache. "Everything happens to me!" he groaned, as he tossed for hours in acute misery. Early in the morning he stumbled down to his workroom, weighed out a little of the *Principium somniferum* that he'd brought from Paderborn, mixed it with sugar-syrup, and gulped it down.

He went back to bed. "If it works on me as it did on the dogs," he told himself, "it ought to put me to sleep in half an hour." It did. He awoke eight hours later, and the pain was all gone.

Well, that settled one thing—the crystals were safe for human

consumption. But now the old fire had started to burn again in his brain, and he remembered the questions which had never been answered. How did this stuff work on human beings? How rapidly did it produce sleep? What was the safe dosage? And how could he answer these problems if he tried the drug on himself and was put to sleep in the middle of the experiment?

He collected three of the town's young daredevils, who assured him they feared nothing, and arranged a night session at the apothecary's.

When the boys arrived, Sertuerner was already there, weighing out portions of his crystals, crouching like an evil sorcerer over his flasks and filters in the dim, wavering light. They stopped short at the door, their courage suddenly gone.

"Hey!" one whispered. "Let's get out of here. I don't like this."

But Sertuerner blocked their escape. "Come in, gentlemen, come in. Everything is ready for us; we shall have a most exciting time!"

"Wait, Herr Sertuerner, we just thought . . ."

"Nonsense, my friends! There is nothing to fear. I'm taking these magic crystals myself." ("And why not?" he thought. "After all, I can stand a bigger dose than these little fellows. I'll be awake long after they're drugged!")

He explained carefully. "I'm giving each of you a little of this powder. I put it, so, into this alcohol. See, it dissolves. And now a little water so we don't burn our stomachs. I assure you, my young assistants, it's perfectly safe—just half a grain apiece you get—and I take the same dose with you—like this. . . ."

The four experimenters, solemn as priests, took their potions.

"Now," said Sertuerner, "please tell me if you feel anything, anything strange. Perhaps . . . maybe you feel a little drowsy? Well, Otto?"

Otto let out a half-witted giggle. "Herr Sertuerner, I feel funny. My face feels hot. But I like it—I feel good, very good."

Sertuerner nodded owlishly, jotted down a note. He watched the three as their faces reddened, their respiration increased, their

elation grew. Half an hour after the first dose they all repeated it with a second half-grain potion.

Quite suddenly Otto no longer felt so happy. His face turned clammy and pale. The other boys, Karl and Hermann, complained of headaches and then of increasing numbness. Even Sertuerner himself felt a little groggy, but he nodded and smiled to indicate that this was perfectly customary, and the boys tried to smile back. They looked, he thought, rather ludicrous. Only fifteen minutes elapsed before he passed around the third dose—again a half-grain.

Things began happening.

Otto slumped to the floor and commenced snoring. Karl tried to stand, fell back on his chair, and dropped his head to the table with a resounding thump; in a moment he was asleep. Hermann decided this was no place for him and headed for the door, but halfway across the room he sat down stupidly on the floor and then sprawled full length.

"Remarkable," Sertuerner mumbled. "You boys fall so hard—you bump your heads—you don't say anything." He clenched his own fist and gave a tentative tap to his head and then a good sharp blow. He could hardly feel it.

Trying to keep his ponderous eyes open long enough to scribble those few last notes, he smiled grimly to see full confirmation of his own previous experience. Then he staggered to the couch, collapsed upon it, and was picked up in a beautiful wavery dream of clouds and soft music.

Later—minutes or hours, he couldn't tell—he realized he was conscious again. He looked around the room and hazily saw the three boys still sleeping. He tried to get up. "O God! My head!"

Then something cut into his groggy mind and told him theirs was no ordinary sleep. Their breathing was peculiar. Their skins looked almost green. That last dose must have been too much. He suddenly became wide awake—perhaps they were all poisoned! Maybe they would die!

"Got to get something!" he muttered. "An emetic—some acid!"

Struggling to his feet, he lurched to the drug room and brought back a bottle of strong vinegar. He forced Karl's mouth wide open and poured the gagging stuff down his throat. Then he did the same with Otto, who protested weakly, and then Hermann, and finally himself.

When he finished and turned around, Karl had already recovered consciousness and was on his hands and knees vomiting. In turn, as the vinegar worked, the others got up, sick and weak, to retch dismally. Karl and Hermann eventually staggered off drunkenly toward their homes.

Otto was too sick to navigate. Thoroughly frightened, Sertuerner dosed him with magnesium carbonate and then carried him home. Otto's mother met them at the door and listened to Sertuerner's confused mumblings and apologies. "Sometime," she said, "I will make you curse the day you came to Einbeck!"

Now Frederick Sertuerner was ready to write his great report. While the townspeople began spreading evil stories about that night's experiment in the apothecary shop, he carefully put all his discoveries and all his knowledge on paper, with a description of the chemical and medical properties of his crystals.

He even gave the crystals a name: remembering the dreams they had produced and thinking of Morpheus, god of dreams, he called them *morphine*.

When the report was finished, he looked for a proper publisher —the devil with Trommsdorff!—and finally sent it to Professor Ludwig Gilbert of Leipzig, editor of the *Annalen der Physik*.

"Nobody but pharmacists would read Trommsdorff's journal," he said to himself, "and pharmacists have no sense of appreciation. But everybody reads Gilbert's—chemists and physicists and even physicians."

Gilbert wasn't too kind to Sertuerner, either. First he flatly refused the report. Then he changed his mind, put it into his journal, and tacked on another of those chilling editorial notes:

"We publish Herr Sertuerner's article against our better judgment. It is highly unscientific and unchemical; if there is such a thing as Sertuerner's 'morphine,' we chemists have much new to learn. . . ."

Sertuerner nearly wept. Again Germany had disregarded her son, but this time Sertuerner had made a wiser choice of editors. Professor Gilbert's journal was read all over Europe, and eventually the morphine report caught the eye of brilliant Joseph Louis Gay-Lussac, professor of chemistry at the École Polytechnique, professor of physics at the Sorbonne, already one of the greatest scientists in France.

Gay-Lussac was ordinarily cold and reserved, but never could he resist a cause that needed a champion. He was tremendously impressed by Sertuerner's discovery and outraged at the treatment it had suffered.

"Were there a number of minor chemical errors?" he asked. "And so what of that? *Mon Dieu*, do we ask this poor pharmacist to be a paragon of all scientific virtues before we accept what he has laid at our feet—a discovery that should be praised by every physician?

"His discovery of his alkaline base, morphine, appears to us to be of the greatest importance. Furthermore, we have repeated some of the author's work and have found it exact.

"We do not fear to propose that the discovery of morphine will open a new field, giving us precise information on the active principles contained in many plants and animals."

And he pounded this home in his lectures at the polytechnic school and at the Sorbonne. "Read what M. Sertuerner has discovered in opium. Read about his morphine. See what this scientist has accomplished without help, without funds, without training, with the most simple apparatus. Gentlemen, this M. Sertuerner can teach all of us how to perform experiments!"

Gay-Lussac started the parade. In a few weeks Germans discovered that their little Sertuerner was famous in France, his

name whispered with respect in the great schools of Paris. He was welcomed into the German Mineralogical Society by the immortal von Goethe; he was given an honorary degree of doctor of philosophy by the University of Jena; he was honored by Berlin, Marburg, Saint Petersburg, Batavia, Paris, Lisbon.

"Well, at last!" he said. "Now I am famous."

But the fame lasted piteously few months. In Germany and particularly in France, little men crawled out of their holes and saw the glory heaped on Sertuerner. "Wait!" they called. "We discovered this morphine first. Sertuerner has cheated us!"

They shrieked their claims louder and louder, and with each attack poor Sertuerner cringed in despondency. How could he battle these people?

And then his second champion appeared.

One Frenchman, backing the cause of a "defrauded" Parisian pharmacist, went too far. He penned a terrific defense for his man and a scathing attack on Sertuerner; he ended his denunciation with the words, "So I reclaim the glory of this important discovery *for France!*"

That did it. Those words reached the office of Professor Gilbert in Leipzig, the very same Gilbert who had once published Sertuerner's manuscript "against our better judgment."

Gilbert read the denunciation and slammed it to the desk. "For France!" he roared. "Ach, for France! So, these French robbers, they'd try to cheat a defenseless German! I'll *show* those scoundrels, those thieves, those unprincipled libelous cutthroats! . . ."

And he wrote a defense that was a masterpiece of eloquent, inaccurate rage—*plagiarists,* he called them, and *liars,* and *men unworthy of the name of scientists,* and on and on.

Did others claim to have discovered morphine first? Gilbert proved that was impossible. Did others wrest painkillers from opium? Gilbert showed their products were useless. Such products were not morphine.

It was a wonderful battle, thoroughly unscientific, with fac

completely ignored, while the combatants pounded desks and hurled insults and demanded revenge for sullied national honor. Sertuerner hadn't the remotest idea of what it was all about. Finally France itself rendered the decision by awarding him the Monthyon prize of two thousand francs "for having recognized the alkaline nature of morphine and having thus opened a way which has produced great medical discoveries."

The honor and all that money, about five hundred dollars, went to Frederick Sertuerner. But the battle for priority had raged too long, and the prize was much too late. Back in Einbeck the tongues had wagged effectively, and whispers had turned into lawsuits. Sertuerner was no match for the combined attack of slanderous neighbors and envious competitors; he fled from Einbeck to a new home in Hamelin.

(The old Pied Piper might have laughed, for here was a man whom the rats had driven to Hamelin!)

For twenty years he lived there, married, and raised his family while he grew completely disillusioned, bitter, and old. People forgot his great discovery so soon. "Morphine?" they said. "Oh, we've always had morphine."

He sat back now, a carping critic content to sneer at the researches of others and to make a few wild guesses himself, including the brilliant theory that boiled water will not transmit cholera. People laughed at him on the streets and called him the distinguished madman.

At the age of fifty-seven he began to suffer with terrible pain, the pain he had conquered so brilliantly for others, but he was barred from the benefits of his own morphine; he became so weak that he could not swallow it, and there was no hypodermic needle then which could have quieted his last days.

One of the greatest benefactors to humanity, the man who turned treacherous opium into pure and reliable morphine, who started doctors on the way to use pure drugs, died forgotten and friendless in 1841.

III

During the years before his death, Sertuerner had paid little attention to the climax of another opium drama being enacted on the Oriental stage. For nearly a century, Chinese and Europeans had been following a path that led inevitably toward trouble. First the Portuguese and later the English and Dutch had forced opium on China. Then in the early 1800's the Chinese Imperial Government awoke to the horrors of the opium habit.

"Opium shall no longer be imported," the government declared, "and it shall not be smoked."

But opium had become big business, and English merchants, particularly the powerful East India Company, either bribed their way around the edicts or ignored them completely. Smuggling opium over ships' sides was perfected to a nicety. Chinese officials closed their eyes to the trade. A few Chinese merchants refused to participate, but most reputable firms yielded to temptation. "After all," they said, "opium is an excellent medium of exchange and much more satisfactory than silver dollars."

Some Englishmen, together with a few Americans, Portuguese, and Parsees, salved their consciences by pointing to this attitude of honorable Chinese merchants. Others claimed they were merely giving the Chinese what the latter wanted.

But no matter what their justification, the smugglers made their activities more and more efficient. They brought increasingly larger loads of the precious poppy juice from Persia, Turkey, Bengal, Calcutta, and a dozen other ports on the Persian Gulf and the Indian Ocean. They built fast boats to outsail clumsy Chinese war junks. They established regional depots at Macao and Whampoa, near Canton, and many an opium rendezvous along the Chinese coast.

Before 1820 the imports rarely exceeded four hundred tons of opium a year. Within twenty years they passed the three-thousand-ton mark—three thousand tons of the finest opium produced in

the world. The amount of domestic opium prepared in China itself was insignificant.

In the middle of the 1830's, however, there were many signs that China was getting ready in its slow, ponderous, and sometimes blundering way to take action. Memorials and petitions were exchanged with increasing frequency. Tension grew between the Imperial Government at Peking and the Chinese Viceroy at Canton. A few foreign merchants, too obstreperous in their smuggling, were ordered to leave China. A few Chinese smugglers, caught redhanded, were either decapitated or, if they could show good excuses for their illicit acts, merely strangled.

Then the British authorities made the move that was eventually to force hostilities. Lord Palmerston, brilliant and caustic head of the Foreign Office, sent a new Chief Superintendent to Canton, one Captain Charles Elliot. Officially, Elliot was to be the highest ranking English representative in China. Actually, his drawing-room personality, ideal for London society, made him the worst possible choice for diplomatic work in the Orient.

Lord Palmerston warned him to be stern and aloof, to mind his own business. Elliot, however, was convinced he could prove superior to the Chinese in their own game of diplomacy and tried to be "strategically friendly." He offered to take any measures to get close to the Viceroy in Canton; the Viceroy not only considered him an inferior but refused to answer his cordial letters. Elliot offered appeasement and asked for equality and thereby left himself open to insults, which he promptly received.

Palmerston received reports back in London and cursed his emissary. "The blundering fool," he rasped. "I told him to keep his place and not to seek openings. By asking favors he'll get himself thrown out of China!"

The warnings were correct but too late. Captain Elliot had already been told to leave Canton and stay in Macao.

The Viceroy was now convinced he could strike a deathblow against the opium trade. More and more Chinese opium merchants

were caught and executed. Trade of any kind, in tea or spices or silk, was allowed one month and banned the next, and the European merchants squirmed under these new laws. But these were merely the beginning. Orders soon came from Peking: "Require all foreigners to surrender any opium in their possession and to sign bonds for their future collective good conduct."

The foreigners rebelled. Under these new edicts, all of them would be forced to put up outrageously high guarantees, all to be forfeit if any single foreigner engaged in the opium trade. No white merchant would trust one of his fellows that far. They tried to leave Canton, but new orders kept them locked in the city. They appealed to Captain Elliot as the official representative of Her Majesty's Government.

The Captain now had the opportunity to be strategic. His decision, however, was to bow gracefully; he urged British merchants to obey as ordered. Then, like a punished small boy, he tried to get revenge. He placed an embargo on any British trade with China. That, he thought, would bring the Chinese to their senses.

The Chinese couldn't be bluffed that easily. They expelled all Englishmen from Canton and from Macao as well. They were nearly ready to expel all foreigners from all of China. Elliot had once been rather impressed with his own diplomatic ability. Now events were crackling about his ears entirely too fast. It was time for the incident.

At Hong Kong a band of English sailors brawled with a mob of Chinese on the water front. When the fight was over, a Chinese lay dead, and the Hong Kong officials demanded that the British fleet release the murderer for trial. The English refused. The Chinese demanded again, and the English refused again.

The Chinese said, "Give up the murderer or get out of China forever."

The English said, "Go to the devil!"

The Chinese opened warfare.

It was a horrible war, like all wars, and as usual the two sides

fought for different reasons. China went to war to wipe out the opium terror once and for all, with no idea that anything else might be involved. England fought for extraterritorial rights. No matter what crime was committed, no matter where it was committed, an Englishman must have the right to fair trial in English courts. To England, the opium was no more important than was the tea in Boston Harbor sixty years before.

It was war, nevertheless. One-sided, with the final outcome never in doubt, it lasted for three years. At the end, the Treaty of Nanking gave to England the city of Hong Kong, opened five ports to English merchants, and made China pay ransom for the city of Canton. Opium, incidentally, was declared a legal article of commerce.

England had won her war for extraterritoriality. China had lost her war against opium; never again did China have the chance to stamp out the curse of the white man's drug. The English and later the Japanese saw to that.

IV

The Treaty of Nanking was signed in 1842. Ten years later opium flashed in the headlines again. In England, Dr. Alexander Wood had been seeking a better and quicker way to get morphine into the blood stream. He succeeded by developing the hypodermic needle. Without fuss or trouble he could inject a few drops of dissolved morphine under the skin, and his patients slipped out of their excruciating pain in a matter of seconds.

Good Dr. Wood was paid for his ingenuity with world-wide acclaim.

He paid back by watching helplessly as a strange and terrible fate overtook his wife. Mrs. Wood, thanks to her husband's discovery, became the first morphine addict to acquire the habit "with the needle."

This was something the brilliant chemists and the ingenious physicians had overlooked: Morphine possessed two edges. The

old Chinese could have told them that, for they had written centuries before about opium and pointed out with dreadful clarity, "Though its effects are quick, great care must be taken in using it because it kills like a knife."

Mrs. Wood's tragic death from morphine addiction should have been a warning, but somehow it was overlooked. Moreover, for no conceivable scientific reason, physicians became convinced that the hypodermic needle provided the one protection against what they called the morphine appetite.

They said, "If we give morphine by mouth, we have trouble. We have to wait too long to get effects. We never know exactly how much to give, since each patient differs in letting the morphine pass from the stomach into the blood. And when we give it by mouth, morphine might start this 'appetite' or even harm the patient.

"But, now, if we give it through Dr. Wood's fine little needle—ah, that's different! We know exactly how much to give, we get results much quicker, and we *never* produce the habit!"

So much for scientific observation.

Some physicians went still further and said, "Morphine addiction? Rubbish! No worse than a liking for alcohol, say, or even coffee."

And so, anointed with the blessings of the chief physicians, morphine was pumped into the veins of any patient who professed a bit of gout or rheumatism or even a toothache. It was the time of America's Civil War now, and army doctors were exceedingly liberal with it. If there were a few who wondered about the agony that followed cessation of morphine injections, well, the poor boys were suffering so from their bullet wounds, and a little morphine meant so much to them. . . .

When the war ended, there were a good many of these "boys," men now, who continued taking the injections long after their bullet wounds were healed. To help them and to save themselves long trips, many thin-conscienced doctors not merely prescribed

morphine but also suggested that their patients keep hypodermic needles at home to give the injections themselves.

Not all doctors remained so blind. Some wrote articles in the medical journals, sent vitriolic letters to newspapers, demanded action from legislatures. And when they began to produce facts—clear, stinging, eloquent facts—the entire medical profession followed their call.

Struck by this onslaught, legislators pricked up their ears. "Morphine? Opium? Addiction? What on earth do you want us to do?"

The doctors told them. "Pass laws. Stop opium and morphine at our ports. Don't let them be given except by a physician. And see that physicians use them only for patients who must have relief."

The doctors had made known their wishes a little too late. Ten years before, they might have had their laws, but now the legislators were also listening to other and more persuasive demands. The patent-medicine folks had discovered that people wanted morphine.

Patent-medicine companies made things easy for such people. They filled newspapers and magazines with seductive advertisements. They plastered billboards and building walls and country barns with fraudulent claims for "painkillers," "cough mixtures," "women's friends," "consumption cures"—most of them loaded with opiates. They provided smartly labeled remedies for colds, "pelvic conditions of women," cancer, rheumatism, neuralgia, diarrhea, cholera, even soothing syrups for babies. The labels gave no warning that opium or morphine was the essential ingredient.

And with a number of doctors, both licensed and unlicensed, they established drug cures, "remedies" for drug addiction which themselves contained morphine or some other opium derivative.

Here was a great business, a business that was giving the public what they wanted. Could any legislature dare interfere with such sanctified affairs? A few states, wiser or braver than most, did dare; most decided to give the matter further thought.

And then, just when medical knowledge of opium was beginning to make sense, just when doctors were really discovering what damage opium and morphine and the other opium-chemicals could do, there came another tragic step. This time the doctors themselves made the mistake.

In 1898 Professor Heinrich Dreser of the Bayer Works reported to the Congress of German Naturalists and Physicians that he had created in his laboratory a new chemical, a cousin of morphine.

A new morphine derivative? There had been lots of them. His audience remained bored.

"Furthermore," said Professor Dreser, "this drug can relieve pain just as well as morphine."

"As well as morphine?" mused his audience. "If that's all, why bother? Morphine is good enough."

"And furthermore," Professor Dreser went on, "my drug is not addicting." Here the audience sat up. "I have used it," he said, "to cure morphine addicts. It prevents pain, produces sleep, and is definitely not dangerous!"

Now the assembled doctors roared out their acclaim. "Here," they said, "is a discovery! Here is a chemical we can use on our patients to stop pain, even to cure them from the morphine habit. Here is a drug that is not habit forming."

"And what," they asked, "is this new miracle?"

"Well," explained the professor, "chemically speaking, it ought to be called di-acetyl-morphine. But that is too complicated for ordinary language. For short we call this heroic drug—*heroin!*"

Probably no remedy was ever heralded so enthusiastically as was heroin. Everything combined to put it immediately into every doctor's kit—the constant calls he had to relieve pain and induce sleep, and his fear that addiction might follow the use of morphine.

Everyone liked heroin. It certainly did what Dreser claimed. And Dreser deserved—well, let's see what prizes would really show our appreciation. . . .

Unfortunately, nobody listened to that man Strube at Berlin's University Medical Clinic. He warned that even heroin might be

addicting, but who was he? Just a research man with no practical experience, no judgment, and certainly no sense at all to make claims like that without proof!

Four years went by, and heroin was even better than anyone had dreamed, and Dreser was still a scientific hero. And then a young medical student, Jean Jarrige, turned in his thesis to the University of Paris. It was titled *Heroin-mania* and listed just a few of the patients whom Dr. Jarrige had seen, men and women suffering a heroin addiction even more hellish than morphine addiction. But who was Dr. Jarrige? No one had ever heard of him.

No one had heard of Dr. G. E. Pettey, either, or had seen his little obscure warning in the *Alabama Medical Journal.* No one heard of the dozens of men who spoke against heroin in those years.

But suddenly the whole amazing affair exploded. Montagnini in Italy lashed out at heroin. Sollier's scathing report came from France. The reports flowed in from England and Germany and Russia, from all over the world; heroin at last stood exposed.

Now the legislatures could delay no longer. In America the Pure Food and Drug Act was enacted in 1906; the Harrison Narcotic Law, in 1914. The laws are rigid, their enforcement ironbound. Today they almost bar experiments to find an agent better than morphine, but they also protect patients against anything more dangerous.

The story of heroin taught scientists and physicians a fearful lesson. Was heroin safer than morphine? The official reports put it in plain words: "The toxicity of heroin, according to all evidence, is greater than the toxicity of morphine. As an addicting drug, it probably exceeds any agent known to us at the present time. . . ."

And there was rule number one for the drug-scientists and for the doctors, too—*You shall not administer to a patient any drug which is more dangerous than the disease which afflicts him!*

CHAPTER II

The Amazing Alkaloids

PELLETIER AND QUININE

KING Philip IV fell heir to the throne of Spain in 1621 only to discover that his legacy was sadly moth-eaten. Portugal was almost gone, Italy ignored Spanish dictates, and the Netherlands clamored for freedom. At home there was corruption and misrule, and abroad the French, the English, and the Dutch were making painful inroads on Spanish commerce.

One Spanish possession, however, was still intact—the most colossal colonial empire the world had ever seen, an empire stretching from the tip of South America to the Gulf of Mexico. Philip put control of that vast territory into the hands of one man, Don Luis Geronimo Fernandez Cabrera Bobadilla y Mendoz, hereditary Alcalde of Segovia, Count of Chinchon, and lord of eighteen villages in the kingdom of Toledo. The Count, a widower, promptly took a new wife, sailed for the Americas, and in January, 1629, made solemn entry into Lima, capital of Peru and center of Spanish power in the New World.

The Count and his Countess ruled in Lima for eleven years. Often during that period he was attacked by a devastating sickness which first made him hot and feverish and then shook him with terrible chills. This was no new disease to him, for he had seen it in Madrid and Seville and on his own swampy farms along the Tagus and the Tajuña. It was no new ailment to his physician, Don Juan de Vega, who reported each time, "It is the malaria."

Knowing of no other treatment, de Vega invariably proceeded to bleed the poor Count.

The Countess, however, seemed to be spared from malaria and often appeared in her husband's place at various pageants, celebrations, and bullfights.

Eventually the king granted permission to his viceroy to leave the New World, and the Count and Countess started on the long journey back to Spain. The Countess never completed that journey; even before she reached the fleet which was waiting at Panama, she was stricken with some mysterious ailment. On January 14, 1641, she died and was buried in the little cemetery at Cartagena, Colombia.

It was at about this time—perhaps a little later but quite possibly a few years earlier—that European doctors began hearing of a magical new cure for malaria, a bark from a tree that flourished in Peru.

"In the district of the city of Loxa," wrote one learned authority, "grows a certain kind of large tree, which has bark like the cinnamon, a little more coarse, and very bitter; which, ground to powder, is given to those who have a fever, and with only this remedy, it leaves them. Having taken a quantity of this powder, to the weight of two *reales,* in wine or in some other liquid, soon after it reduces the temperature. . . . These powders are now very well known and esteemed, not only in all the Indies but in Europe, and are urgently sent for and demanded from Rome."

Such a cure for fever might well be "urgently sent for," since malaria was known only too well in Italy and Greece, in Spain and France, in Belgium and Holland, and even in England.

How did this remarkable bark first reach Europe?

Within a few years, there were so many explanations that it was impossible to tell. One historian declared that it was Don Juan de Vega, physician to the Count of Chinchon, who had brought the bark to Spain and there sold it for much gold; but de Vega never returned to Spain and instead remained in Peru as a professor at the university. Another authority declared that the bark had been brought by the Count, himself, after it had cured his fever; but, according to his diarist, the Count knew

nothing of the bark and certainly nothing had cured his fever.

Most widely believed was the legend that it had been the Countess of Chinchon who had been cured from malaria by the bark, who had then distributed bark to malaria victims in Lima, and who had finally brought it to Spain and there dispensed it to the feverish peasants on her husband's estates. But the Countess apparently never suffered from malaria, never was cured of malaria, and never went back to Spain, with or without bark.

This last explanation was not accurate but it was at least romantic. It was therefore accepted for three hundred years.

No matter how it arrived in Europe, however, this new fever bark was made truly welcome. It was one of the greatest gifts nature had bestowed on mankind, a cure for malaria. It was the first specific cure of any kind that had yet been discovered. With the whole world helpless against malaria, Spain looked upon this miraculous new drug not only as a boon to medicine but also as a financial godsend. The early shipments from Peru were sold at more than their weight in gold.

"Why," asked the Spaniards, "should we seek and dig for gold when this precious bark grows so abundantly in the forests?" And so the bark trade began.

It began in the city of Seville, which had a monopoly on imports from the New World, and then spread like wildfire throughout Spain, Italy, France, the Netherlands, and England. The bark saved young Louis XIV of France, papal officials in Rome, and noblemen in London. It was distributed to rich and poor by the Jesuit fathers; that started the trouble.

As long as the powdered bark was called "Peruvian bark" or "Powder of the Countess," all was serene. But when the Jesuits began to dispense the drug, it became known familiarly as "Jesuit's Powder." That was a mistake.

People were suspicious in those days, so suspicious, in fact, that good Protestants absolutely refused to touch Jesuit's Powder and preferred to die with their malaria intact. "This Jesuit's Powder

is dangerous!" they whispered. "It's part of the Pope's diabolic plot to rid the world of non-Catholics!"

Doctors, of course, laughed at such baseless superstitions, but they had their own problems to solve. "Is it really wise," they pondered, "to substitute this new, unproved drug in place of such well-known, time-tested remedies as viper's broth or crab's eyes or murderer's skull?"

And further, "This bark cannot be very useful. After all, Galen's great textbook of medicine lists all the good drugs, and it does not list Peruvian bark."

True enough, it wasn't listed by the omniscient Galen who wrote his book fourteen centuries before Peruvian bark reached Europe! So doctors, thousands and thousands of them, ignored this slight discrepancy of fourteen hundred years and were perfectly content to let Galen's dead hand reach out of the grave and strangle medical progress. The popular fear of being "Jesuited to death" was not half so serious as this crippled thinking of physicians. For the first time since the third century, Europe's medical men were forced to make up their minds—what should they believe, the things they were taught or the things they saw?

A few slabs of bark from Peru had brought medicine to a crisis.

A year after the Countess of Chinchon had died in South America, Robert Talbor was born in Cambridge, England. He appeared for a while as a medical student at St. John's College in Cambridge but never got around to completing his course. At the age of twenty-one he turned up as an apprentice in a Cambridge apothecary shop, and from Cambridge physicians he learned about the bark controversy. He vanished from Cambridge and appeared as a full-fledged physician (without benefit of training) in Essex and then in London. He wrote a little book on the art of curing malaria—a book rich in claims but poor in facts.

Certainly nothing in Robert Talbor's early history warned the world that here was a man to be watched. He was a quack, but in London there were hundreds like him.

Suddenly the College of Physicians awoke to discover a veritable catastrophe. Talbor had inconspicuously wormed his way into polite society and into royal circles. He had cured the feverish daughter of noble Lady Mordaunt, and he had even cured the King of malaria. This was outrageous enough, but it wasn't the end: Talbor had got himself knighted and appointed official physician to His Noble Majesty Charles II, King of England.

The College of Physicians exploded. "The appointment must be a mistake!" they cried. "The King has been tricked by false friends. This scoundrel Talbor must be taken in hand immediately and removed!"

But this "scoundrel" was no fool. He had used his friends at court to snare the appointment for him, and now he put them to work again. When the dignified delegates requested an audience, they were turned down. "Sir Robert Talbor has indeed been appointed by the King," they were informed. "And he will be kept by the King!"

Supported by a title, a position at court, and the favor of the King, Talbor was now ready for business and proceeded to concoct a wonderful secret remedy to cure fevers. It was potent, well advertised, equipped with suitable testimonials, and not too expensive. It sold in vast quantities.

"My remedy," he claimed, "is a safe and worthy substitute for Peruvian bark. The bark, which is known to some as Jesuit's Powder, may be a noble medicine when given properly, but it has dangerous effects when administered by the unskilled. On the other hand, my remedy is always safe. It is infinitely better than Peruvian bark!"

Better than Peruvian bark? That was most unlikely since Talbor's preparation *was* Peruvian bark; but, of course, only Talbor knew that.

After seven years of monopolizing fever cures in England, Talbor sought new fields to conquer and went to Paris where the dauphin lay stricken with malaria. The court physicians had tried everything—everything, obviously, but Peruvian bark—without

success. To the distress of the good French doctors, the gallant Englishman stepped in, cured the noble patient, and became the national hero of France.

King Louis XIV, the prince's father, was grateful. "We give you our royal thanks," he told Talbor, "and you will find us generous. How may we repay you for your services?"

Talbor bowed gracefully. "It was a privilege, Your Majesty, to serve the glorious King of France. Your gratitude is payment enough!"

"Ah, indeed. Very nicely expressed," said Louis. "But pray inform us. We understand that our son was saved by a secret remedy. What is this magic cure?"

"Oh, it is but a simple mixture that I have prepared, Your Majesty."

The King frowned regally. "Do our French physicians know its constituents?"

"No, Your Majesty."

"A great pity. Could you divulge the secret, Monsieur?"

Talbor took a deep breath. "I deeply regret that . . ."

"Ah-h-h!" said the King. "We understand perfectly. Very well, Monsieur, it is our royal pleasure to bestow upon you the title of Chevalier of France, together with a pension as long as you live and two thousand louis d'or. And now, Monsieur, the remedy?"

Talbor smiled. "I was about to say, Your Majesty, that I deeply regret I do not have a description of the remedy on my person. I shall have it in your possession within an hour."

It was a good bargain for Talbor, particularly since the King agreed to withhold publication of the prescription until Talbor's death. But for Louis it was an expensive loss of memory. Had he but recalled, he himself had been cured of malaria forty years before, and the remedy in that case, too, had been Peruvian bark!

A year later Talbor died in England at the age of thirty-nine, and immediately King Louis printed the prescription. The secret was out. The magic remedy consisted of six drachms of rose leaves, infused for four hours in six ounces of water, with two ounces of

lemon juice and a strong infusion of Peruvian bark. The prescription also contained Talbor's detailed and excellent directions for administration.

One glance at this formula made the French doctors feel exceedingly sheepish. It was all too obvious that the rose leaves and the lemon juice were mere camouflage. The bark, which they had battled for so long, was actually the cure. Within a few years the French physicians and later those in England and the rest of Europe forgot the fights and squabbles and put Peruvian bark on their lists of accepted remedies.

A dapper quack had smashed fourteen centuries of stifling conservatism.

II

For half a century after Talbor's death and the exposé of his secret, the history of Peruvian bark ran smoothly. The few diehards who opposed its use were finally ignored. In honor of the long-dead Countess of Chinchon, botanists changed the name of the bark to *cinchona.*

Then, in the middle of the eighteenth century, a few workers in scattered European laboratories started to pry into this cinchona. Some were scientists who wondered what the bark contained; others were practical men who sought a way to distinguish between pure cinchona and adulterated products.

First came a shower of false claims—from Sweden, France, Germany, Portugal, Russia, and Scotland—reports that pure chemicals had been found in cinchona and that these chemicals cured malaria.

In Paris one Armand Seguin—war profiteer, drug adulterator, and former inhabitant of the Bastille—announced the remarkable (and completely fallacious) discovery that good cinchona bark was rich in gelatin. "It is this gelatin," he claimed, "which is the active principle. It is gelatin which cures malaria!" But gelatin doesn't cure malaria. Eventually Seguin found that out himself. So

did the poor doctors who took his recommendation and drugged their malaria patients with such gelatin products as purified glue.

Next came the notorious Antoine François Fourcroy, the French professor who surpassed all his competitors or had them sent to the guillotine. He went through a long series of chemical manipulations and pulled out of cinchona a dark-red, odorless, tasteless mass which he called "cinchona red." Contrary to his claims, it had no effect on malaria. Nevertheless, Fourcroy stood on the edge of a magnificent triumph and gave up too soon. "These researches," he concluded, "will no doubt lead to the discovery of the anti-malarial substances."

He was absolutely correct. A few more days' work and he would perhaps have made that stupendous discovery himself.

Then one afternoon in Paris, two young chemists met in a pharmacy laboratory and proceeded to make scientific history. One was Pierre Joseph Pelletier, twenty-nine-year-old son of a pharmacist and already professor at the high school of pharmacy. The other was Joseph Bienaimé Caventou, twenty-two, a brilliant, irrepressible pharmacy student.

The two met first in 1817, the year Sertuerner's great morphine report was published. They read that report and devoured every word of it.

"That man's method is admirable," Pelletier had said, "so simple and yet so powerful. If he can find his morphine in opium, perhaps we can find active chemicals in other plants."

They began with ipecac, a new product introduced from South America as an emetic and a cure for dysentery and diarrhea, and isolated from it a pure chemical which they labeled *emetine*. Then they turned to the poisonous strychnos plant and extracted a chemical which caused a horrible death preceded by convulsions, spasms, foaming lips, and a terrifying frozen grin (the "sardonic grin" named after Sardinia, home of the strychnos plant). Pelletier and Caventou planned to call this chemical "vauqueline" in honor of their good friend M. Vauquelin, but mutual friends advised against it. M. Vauquelin, they said, might not appreciate the honor

of having his name attached to such a deadly poison. Instead the new chemical was named *strychnine.*

Laboratory tests showed that both emetine and strychnine resembled Sertuerner's morphine. They all worked like alkalies, reacted like alkalies, had all the properties of alkalies, but did not have the formula of alkalies.

"Here is a whole new family of chemicals," proclaimed chemist Meissner in Germany. "They are all plant products, organic chemicals that are very much like alkalies. They might well be called *alkaloids.*"

Soon Pelletier and Caventou discovered another of these alkaloids, *brucine,* in false angostura bark, and simultaneously with Meissner they extracted *veratrine* from sabadilla seeds. Other workers found *piperine* in pepper and *delphinine* in delphinium plants.

Now Pelletier, above all things, was a practical Frenchman and a practical pharmacist. "These lovely new alkaloids are very interesting," he said, "but they are not practical. Who will buy them? Strychnine, brucine, veratrine, and the rest—they are but scientific curiosities. No one will waste a franc on them. It would be most satisfactory if we could find something more valuable."

Caventou supplied the lead. This young man was forever asking questions, sticking his nose in the wrong places, butting in and bothering and annoying, picking up an amazing collection of miscellaneous information, learning—and remembering—isolated facts and phenomena. He seemed to be doing a hundred things at the same time, even while thinking of a hundred others.

While he was collaborating with Pelletier in his research, Caventou was also studying under Professor Thénard. One day in the professor's laboratory, another of Thénard's assistants commented on cinchona bark.

"I've run across a very funny thing," remarked this assistant. "M. Thénard asked me yesterday to make up an extract of cinchona for him to demonstrate before his class. Now, it looks to me as if this cinchona extract is extremely alkaline; why, when I . . ."

Caventou pricked up his ears, then quickly removed his laboratory apron, snatched up his hat and coat, and scampered over to see Pelletier.

"Pierre," he announced, "we must start work at once on cinchona!"

The senior author was slightly startled. After all, it was his place to suggest the work to be done. "And just why," he asked coldly, "must we study cinchona?"

"Because it is a most important drug," Caventou explained. "It cures malaria, and malaria kills thousands, perhaps millions of people every year!"

"Well," replied Pelletier, "if that's the best reason, we might as well study consumption or plague or the smallpox. They kill millions, too."

Caventou shook his head. "That may be true, but malaria. . . . Look, this cinchona cures malaria. We know that. We can start from there; and in cinchona there is an alkaloid. . . ."

"Wait!" Pelletier exclaimed. "What's that you say about an alkaloid in cinchona? Where did you hear that?"

"From M. Labillardière, over in Thénard's laboratory. He's one of the assistants. He told me only this morning that he made an extract of cinchona, and the extract gave alkaline tests!"

Pelletier grunted. "Alkaline tests, is that all? Why, that doesn't mean a thing. There might be some impurity in there, some lime or potash or soda. It doesn't necessarily prove there's an alkaloid in cinchona . . . but on the other hand. . . . Hmmm! Joseph, my friend, let us examine the literature on cinchona. . . ."

They got out the old books and journals, and they read the details of experiments which had been performed years before in Sweden, in France, in Germany, in Scotland, and particularly by Dr. Gomez in Portugal.

All these men had found chemicals in cinchona bark, strange chemicals, but nothing that would cure malaria and nothing that seemed to be an alkaloid. That, however, was hardly surprising since they could not have been looking for alkaloids then.

Perhaps some of these early experiments might be repeated, suitably modified to conform with the newest discoveries of Sertuerner and themselves.

But which of all these researches should they repeat? They studied them all again and finally decided that Dr. Gomez' work looked the most promising. They memorized his procedure, added a few improvements of their own, and went to work.

It was ridiculously simple. Whereas Sertuerner had worked for years to isolate morphine, these two Frenchmen completed their work in a few days. They extracted gray cinchona bark with alcohol and added a little water and then a bit of potash. Tumbling out of this clear solution appeared a fine batch of white crystals.

These crystals were redissolved and reprecipitated again and again until they were clean and shining white. These, the beaming scientists felt, must be the pure alkaloid, the curative principle of cinchona!

But how wrong they were. In spite of their improvements, their modifications, and their better technique, their shining white crystals were the same thing that Gomez had found years before. If they had stopped there, they would have ended with merely one more cinchona constituent that wouldn't cure malaria.

But Caventou, that living storehouse of ill-assorted information, came to the rescue. "Wait," he said, "let's do one more thing before we start writing the report. We've got our results on gray bark. Let's try the same thing on yellow cinchona bark."

"What!" retorted Pelletier. "Why should we waste time doing that? Gray bark, yellow bark, they're all the same. They're all cinchona bark."

"No, they're not. I know a man who . . ."

"Bah," said Pelletier, "you always know a 'man who' something or other!"

"Now, wait a minute," Caventou interrupted. "This fellow knows what he's talking about. He's a doctor. He wrote a book on malaria and he said . . . now, what did he say? Oh, yes, that these cinchona barks aren't the same at all. At least they don't work the same

on malaria. He said that yellow bark was pretty good, but this gray bark that we used doesn't cure the fever nearly so well. See?"

"See? See what?" asked Pelletier.

"Oh, name of a thousand names!" Caventou scratched his head in disgust. "Look, I'll tell you again—slowly. We find these white crystals in gray bark. Right?"

"Right."

"All right. But gray bark is poor and yellow bark is good. Now, how do we know what's in yellow bark? Tell me that, if you will."

"Well," admitted Pelletier, "we don't know. How can we know if we haven't looked?"

"That," sighed Caventou, "is what I've been trying to tell you!"

So they looked. On a fresh supply of good yellow bark, the best they could find on the market, they repeated their original experiment—going through the same maneuvers, adding the same reagents, and getting nothing. No crystals, no shining white precipitate. Nothing but a sticky, pale, yellow gum that wouldn't crystallize no matter what they did to it.

It was bitter, this gum, as was their first product. Similarly, it was soluble in acid and in alcohol. But, unlike the first one, this gum was also soluble in ether. It was certainly a new chemical.

They described their discovery in 1820, when Pelletier was thirty-two, and Caventou only twenty-five. To their new product, another alkaloid, they gave a name taken from the old Peruvian Indian word *quinaquina* which early Spanish botanists had erroneously applied to cinchona. They named the new drug *quinine.*

Here was a pure chemical to cure malaria.

At first the two pharmacists weren't sure of that. All they had were a couple of chemicals, and it was not their job to test them on human beings. They merely concluded their report with the hope that some skillful physician, "joining prudence to sagacity," would make the necessary clinical tests on patients.

These "prudent and sagacious" physicians were not long in appearing nor in discovering the first product worthless while quinine was remarkably effective. There was one, François

Magendie, a distinguished physiologist and physician, who had already been courageous enough to test morphine, iodine, bromides, strychnine, brucine, veratrine, and emetine on patients; now he added quinine to the list and used it in his own practice. At the same time, a French army officer, Dr. Maillot, tested quinine in Algiers and Ajaccio. Both the quinine and his ability must have been more than satisfactory, for Algiers named a street after him, a village, and finally voted him a handsome pension.

Pelletier and Caventou took out no patent on their discovery, although such an act would have been perfectly customary, but they were richly rewarded by their country. They were given distinguished appointments, high honors, and the coveted Monthyon prize of ten thousand francs. France even set up a statue to Pelletier.

After a brief pause for refreshments, compliments, and salutations, the scientists went back to work. Pelletier isolated four new alkaloids from opium. Other French and German scientists found additional alkaloids in cinchona bark, and the family relationships between all these quinine alkaloids were explained by a budding young French chemist, one Louis Pasteur.

A pair of workers, looking for quinine in coffee, came out with *caffeine*. Others found *coniine* in poison hemlock, *nicotine* in tobacco, *atropine* in belladona, *codeine* and *papaverine* in opium, *ephedrine* in the almost legendary mahuang of China, *scopolamine* (for twilight sleep) in the scopola plant, and *theophylline* (for sick hearts) in tea. This was a perfect torrent of discoveries, but the two men who started the flood were unable to see its crest. Sertuerner, discoverer of morphine, died in 1841 at the age of fifty-seven. Pelletier died the next year at the age of fifty-four.

Sertuerner was forgotten by scientists long before his death, but they remembered the Pelletier family long afterwards. In 1877 a new alkaloid was found in pomegranates and named *pelletierine*. Pelletier would have liked that; for this new chemical was quite practical. It killed tapeworms.

By the middle of the nineteenth century, the world had a fine array of alkaloids headed by morphine and quinine. Quinine was pure, it was potent, it was dependable, and it was so infernally expensive that its benefits were available only to the rich. In 1850 the French Society of Pharmacy called chemists to the rescue:

"It has long been an important question how to obtain a substitute for quinine possessed of the same therapeutic effects or how to reduce the price of its production to permit its employment in all the numerous cases in which its use is indicated. . . . We therefore make an appeal . . . offering a prize of four thousand francs for the chemists who shall discover the means of preparing quinine artificially. . . ."

Contestants were instructed to enter their claims before January 1, 1851, and to send in at least half a pound of the synthetic material.

The prize was never awarded. Other alkaloids were created in the test tube, others were manufactured at a cost much lower than that of the natural substances from trees and plants, but quinine seemed to be hopelessly difficult. When a pair of young American chemists finally succeeded in the synthesis, making artificial quinine in their Boston laboratory, nearly a century had elapsed, the world was at war, quinine had become a strategic raw material, the Nazis were already strutting in Paris, and no French prizes were being sent to the United States.

When the French Society of Pharmacy offered its prize for synthetic quinine, it couldn't possibly have foreseen the results that would follow. It couldn't have foreseen that eighteen-year-old William Henry Perkin in England would try to make synthetic quinine and discover instead, by the sheerest accident, synthetic mauve—first of the coal-tar dyes.

The French pharmacists couldn't have dreamed that the immediate failure to create synthetic quinine would force Europeans to take action against the South American monopoly on cinchona bark, nineteenth-century source of the world's quinine supply.

III

As early as 1750 that monopoly had become obvious and onerous to a few farsighted Europeans, and attempts were made to smash it. There were to be many such attempts and many tragic failures before the world became aware of the cinchona jinx.

First came four Frenchmen who arrived in the city of Quito in Ecuador in 1735. Sent there by the French Academy to measure one degree of meridian at the equator, they were thus to determine the circumference of the earth. Before their measuring had even started, geographer Charles de la Condamine felt he had been insulted and walked out of the expedition.

He traveled south along the Andes and trudged into the lush forests of Loxa, home of the first cinchona trees to be discovered by white men. He visited with a Spanish bark-trader and there learned the financial background of the cinchona industry.

"*Mon Dieu!*" he declared to his host. "This cinchona bark which you collect is so cheap? It costs so little here in Peru? I cannot believe it, for in France such a small bit costs many hundred francs."

"But of course it is cheap here," said the bark-trader. "We just peel the bark from the trees, and there it is. It costs us nearly nothing!"

De la Condamine thought about that. "Why should I not attempt to transplant these valuable cinchona trees to France?" he wondered. "We could peel their bark very easily in Europe, too."

With the aid of his host, he carefully dug up dozens of young seedlings, planted them in boxes of rich soil, and started off to Paris. He struggled over the mountains, came to the Amazon, and began his hair-raising voyage downstream to the Atlantic.

Week after week, he and his Indian companions braved the swamps and the jungle—shooting rapids, skirting waterfalls, eluding hostile natives and dangerous animals, floating thousands of miles without one serious accident until at last they reached the mouth of the river. Then, almost within sight of the boat that

would carry their precious plants to France, their little vessel was nearly capsized by a tremendous wave which washed all the plants overboard.

De la Condamine was lucky he hadn't been drowned himself, but he thought only of his lost treasure. "My poor little plants," he cried, "they are all gone! I have carried them for twelve hundred leagues, for eight long months, and now—nothing!"

Back in Ecuador, the other scientists had said farewell to De la Condamine and proceeded with their task of measuring that piece of equator. When the work was done, they disbanded and started for home. One of them, botanist Joseph de Jussieu, decided to take a look at Peru before leaving South America.

He crossed the Peruvian border just as the natives were fighting a deadly epidemic, and, since he was also a physician, he offered his medical services. When the epidemic was over, he resumed his travels, visited a few towns, collected a few flowers, and stayed there—for thirty years.

"This country is amazing!" he said. "There are so many new plants, such remarkable trees, such a wealth of insects! How can I go back to Paris?"

Year after year, he continuously added to his collection—plunging deep into the forests, climbing to high frozen passes, wallowing through muddy swamps. His collections grew to staggering size, and his notebooks bulged with careful, detailed notes. He posted brief reports to his colleagues back at the French Academy, promising them on his return, someday, to show them the most fascinating specimens in the world.

Finally, after half his life had been devoted to South America, he decided his work was done and he had earned the right to die in his old family bedstead. And he, too, decided to bring living cinchonas back to France.

De la Condamine had tried to bring seedlings to Europe, but De Jussieu selected seeds. He collected his seeds, thousands of them, and put them in a tight little box with a strong lock. He

watched that box every minute as if it contained precious diamonds and rubies. That very care proved his undoing.

In Buenos Aires, where he awaited a homeward-bound boat, a servant watched him guard that little box. So zealous was his care that the servant was convinced that the Frenchman must be guarding fabulous treasure, and one night he stole the box. Finding the "treasure chest" held only worthless seeds, he threw them away in furious disgust.

When he discovered his loss, De Jussieu was frantic with grief. His most prized possession was gone! The authorities made a half-hearted search for the thief, but he had vanished.

The poor little Frenchman sailed for home. His enthusiastic colleagues met the boat with word that his brief but brilliant reports had won him membership in the Academy of Sciences. But De Jussieu was not impressed. He didn't even understand. He was completely and permanently insane.

This cinchona jinx, of course, was pure superstition. De la Condamine and De Jussieu had just been unfortunate. Other explorers, however, were also unfortunate—a Jesuit expedition brought cinchona plants from South America to Algeria, but the plants died. The French and Dutch succeeded in carrying seeds to Paris and to Java, and again the plants failed to thrive.

The Dutch tried again, in spite of growing restrictions against foreign collectors. They sent a distinguished botanist, Justus Hasskarl, to Peru. Hasskarl had troubles: trying to get to the forests at just the right time to collect his seeds, he played hide-and-seek over the Andes; he adopted an alias; he bribed officials and induced natives to do the collecting for him; he held secret meetings near the Bolivian frontier where seeds and bags of gold changed hands.

After two years of this, Hasskarl finally reached the Dutch East Indies. He had brought hundreds of plants, thousands of seeds. The plants failed to withstand the voyage, but then, there were still those thousands of seeds!

The Dutch government was truly grateful to the brave explorer. He was put in charge of the new cinchona plantations in Java. He was made Knight of the Netherlands Lion and Commander of the Order of the Oaken Crown.

But there had been a tragic mistake, or was it the jinx again? The seeds sprouted and grew into flourishing shrubs, and the shrubs were laid out in vast plantations. Only then was the mistake discovered: Hasskarl had brought seeds from the wrong kind of cinchonas. The bark of his particular trees contained no quinine.

Finally the South Americans took official notice of these raids on their monopoly. "God has given us the great cinchona forests," they said, "and we cannot allow them to be plundered. Our most priceless possession shall not be taken from us."

They passed strict laws regulating export of bark from the Peruvian forests (which had already been stripped to extinction) and from the newly discovered forests in Bolivia, Ecuador, and Colombia. In addition the people vowed that no foreigner should steal their livelihood.

"Dead bark can be exported," they said, "but no living seeds, no living plants, nothing that might start a rival cinchona industry outside of South America!"

The South American countries intended to make the most of their God-given monopoly. Now, at last, they could crack the whip!

So millions of malaria victims cried for cinchona and quinine, and the price steadily climbed. . . .

IV

In a government office in London, a young English clerk sat reading the official correspondence on cinchona. He was Clements Markham, twenty-four-year-old son of a distinguished clergyman, but there was nothing at all clerical about him. He had already served four years in the British navy; visited South America, Mexico, California, and the Sandwich Isles; and taken part in the

unsuccessful search for Sir John Franklin, who had disappeared on an Arctic hunt for the Northwest Passage. He had traveled again to Peru and studied the history of the vanished Incas.

He had also spent six horrible months as a clerk in another government office, where he devoted his abundant energy to copying details of musty legacies.

A month before his twenty-fourth birthday, he was pardoned from this deadly routine and placed in a new department. His job now was to assist in clearing information between the English government and the great East India Company. And there he found, buried in dry official reports, the inside story of cinchona.

In Peru he had actually seen the cinchona forests, and now he discovered how valuable they were. He learned that quinine could cure a deadly fever afflicting one-third of the world's population and killing a million victims a year.

He read reports of scientists pointing out that in India and Ceylon there existed mountainous regions with a climate very much like that of the Andes. And he studied the constricting laws governing exports from South America.

For five long years he studied cinchona and South America. He talked to Sir William Hooker, director of Kew Gardens, and to wise John Eliot Howard, the leading quinine manufacturer in England. He talked to botanists, chemists, officials of the India Office—to anyone and everyone who might conceivably know something about Peru or India or cinchona trees. Finally, in 1859, his plans were complete, and he laid them before the Revenue Committee of the India Office.

This was by no means the first proposal for a cinchona expedition which had been placed before the committee, but the members had never seen anything like this. Here was a youth, still in his twenties, who had the effrontery to suggest not merely one expedition, but four simultaneous thrusts, all to be made under his direction, in four different areas. Here was a request for funds and official sanction that was absolutely preposterous!

The sheer audacity of the report turned the trick. This Clements

Markham might be young, but he knew the country, the people, and the languages. His plan appeared to have the backing of scientists and manufacturers. Experts were convinced that the idea of starting cinchona plantations in India was sound.

In an amazingly short time the expedition was approved. The Secretary of State for India gave official authorization to Markham to collect cinchona seeds and plants and to superintend their transportation and introduction into British India and Ceylon.

Markham had shown imagination in planning the campaign and ingenuity in promoting it. Now he showed his brilliance as an executive. In his selection of men to work with him, he couldn't have chosen more wisely. Some were trained botanists, others were experienced explorers; but all of them were filled with a spirit of "do or die" for England—a spirit that brought some of them closer to dying than doing.

Pritchett, an explorer, was to collect the gray-bark cinchonas in the Huánuco forests of central Peru, north of Lima. Dr. Spruce, a distinguished botanist, was to get the red-bark cinchonas in the Ecuadorian Andes. Cross, a painstaking Scotsman, was to assist Dr. Spruce and then get crown barks from Ecuador and the Colombian barks from the Colombian Andes north of the equator. And young Weir, an English gardener, was to accompany Markham on the search for yellow barks in southern Peru.

These men were to move into remote, isolated areas along a two-thousand-mile front. They were to move almost simultaneously, quietly, and as rapidly as possible. Considering the dangers, they felt that some would fail, hoped that at least one would succeed.

Markham, accompanied by his wife and the faithful Weir, landed at Islay, the little desert port on the south coast of Peru. At the British consulate they left their Wardian cases, miniature greenhouses already filled with soil, which were to carry their plants, if any, on the trip home. After a two-day march across the sands, they reached the city of Arequipa. Minna Markham was deposited there with old friends of her husband, while the two men started on the long ascent of the mountains.

It was quite a climb. The tiny mule track zigzagged up the western chain of the Andes through daily snowstorms and sheets of rain to an altitude of nearly sixteen thousand feet. Then there was the drop, down a frozen gorge, across swamps, down more cliffs, and finally into the city of Puno on the shores of Lake Titicaca. They were still two miles above sea level, and there was still another half of the Andes to scale, the towering eastern cordillera.

Using only the wretched, broken-down mules available at post-houses, Markham and Weir left Puno on the road that led to the great Inca capital of Cuzco; then they branched off to the east and started to climb again. There were more towns, thousands of feet above sea level, and more passes, even higher. There were more storms and snow, driving sleet, mud, slippery paths.

At one of their overnight stops in a little shepherd's hut, they met another traveler, Don Manuel Martel, former colonel in the Peruvian army. Martel seemed friendly enough at first and then began asking surprisingly appropriate questions about cinchona.

"Señors," he asked, "did you ever hear of one José Carlos Mueller?"

The two Englishmen shook their heads.

"He was a bad man," Martel continued. "His real name was Hasskarl. He was sent here by the Dutch. He stole cinchona plants to rob my people of their livelihood. You have never heard of Señor Hasskarl?"

Markham kicked Weir as inconspicuously as possible. "No," he answered, "sorry, but I have never had the pleasure."

Martel stared at him. "You don't know him? You are certain? Ah, well, it is of no matter. But if we ever find him or any of his assistants again in my country, we cut off their feet! Ah, you two gentlemen would not be interested in cinchona trees, would you?"

Both Markham and Weir were quite certain they would not be interested in cinchona trees. Next morning Martel started down the path to Puno while the Englishmen continued onward to the beautiful Caravaya valley and the lush forests of cinchona trees.

It had taken nearly a month to reach the Caravaya district and the yellow-bark cinchonas. For another month the two men did their collecting. Their mission could not long remain a secret, and there was no time to lose. Martel, the half-mad Peruvian colonel, had been entirely too suspicious and was spreading dangerous rumors throughout the country. In addition, they were working along the Peru-Bolivian border, and these two countries were threatening to declare war on one another.

Each day they toiled in the forest—forcing their way through dense tangles of brush, skirting stands of exotic palms, kicking away clumps of fern and common orchids, fording rivers, sloshing through yellow mud. Each night, ready to flee for the coast at a moment's notice, they put their collection of plants in Russia-matting bundles.

After four weeks of this precarious existence, Martel's rumors took effect. From a near-by town the municipal alcalde sent orders that the two foreigners were to be arrested and their plants confiscated.

The hour had come to move—and move rapidly.

Markham did take time, however, to write a long, bluffing answer to the alcalde. "As I understand the provisions of the Peruvian constitution of 1856," he wrote, "your functions are purely consultative and legislative, without executive powers. . . . I take this opportunity to express my appreciation of your patriotic zeal. . . . I regret that it should be accompanied by such misguided and lamentable ignorance of the true interests of your country!"

He gave this note to a messenger and urged him to rush it to the alcalde. Then he turned to Weir. "By the time the honorable alcalde reads that," he said, "we'll have the whole Peruvian army after us; but it does give us a few hours' head start. Let's run for it!"

They slapped their possessions together, lashed them on the mules, tenderly added the precious bundles of seedlings, and started down the trail. Before they had gone many miles, they

found a menacing committee blocking the path. Markham whipped out his pistol, flourished it bravely, and the committee withdrew.

"Whew!" he whispered. "Thank God for that. Couldn't have fired the blasted thing—powder's all wet!"

After another few miles, one of the pack mules slipped off the path and dropped on a tangle of brush halfway down a steep cliff. Markham went down to rescue the animal and its pack of cinchona plants, while Weir, who hated to waste even a minute, collected a few more plants from a near-by grove.

At the first town it was apparent that the entire countryside had been aroused. The villagers were no longer friendly. It was difficult to buy provisions and impossible to get pack animals unless—and this was made exceptionally clear—unless the foreigners agreed to return the way they had originally come, via Puno. It was also made clear that another committee was waiting at Puno, a more threatening committee, under the command of Martel, himself.

This discovery altered the situation considerably. It was decided that Weir should take all the animals and a few cinchona plants. Meanwhile, Markham, discreetly trying the threat of his useless gun again, stole three other beasts, which were quickly loaded with the bulk of the plants.

With a few natives and the main part of the caravan, Weir courageously headed toward Puno and the menacing colonel. If Martel wished to destroy the few seedlings in his possession, that would be perfectly all right—so long as he spared his feet!

Markham, however, faced an even more serious problem. With his three animals, a guide who, it later appeared, had never been outside his own village, and most of the plants, he started off to Arequipa on a different course. Using only a compass and the crudest of maps, he intended to follow a straight line over the towering Andes.

Of course it was bizarre, unthinkable, thoroughly and crazily impossible. Yet, ten days after he had left Weir and the main expedition, Markham arrived in Arequipa and safety. Two days later

Weir arrived, minus only his few seedlings, and he and the Markhams moved on to the port of Islay and the British consulate.

The first part of the Markham expedition had succeeded. In a short time, the plants were safely on board the steamer bound for Panama and transshipment to London.

The second part was equally successful. A few months after Markham came out of the yellow-bark district in the Caravaya valley, Pritchett came out of the Huánuco forests of central Peru with a collection of gray barks.

In Ecuador, the botanist Dr. Spruce had collected one hundred thousand seeds of the red-bark cinchonas and sent them off safely to England. He had also collected severe rheumatism and a peculiar nervous malady which resulted in an intermittent paralysis from which he was never to recover.

"Although upheld by a determination to execute to the best of my ability the task I had undertaken," he wrote in his notebook, "I was but too often in that state of prostration when to lie down quietly and die would have seemed a relief. . . ."

The English government paid his salary of $150 a month and gave him $135 for the elaborate report he had prepared. After ten years of effort, Markham finally succeeded in having Spruce given a pension of $500 a year as a mark of his country's gratitude.

The Scotch gardener Cross made more than one expedition. After collecting the crown-bark cinchonas from Ecuador and the Colombian barks from Colombia, he was sent to Panama to collect India rubber plants, to Brazil for hevea rubber, and back to Colombia for cinchona again.

For these important expeditions and for the rich collections he brought back, Markham recommended that he be given at least five thousand dollars. That in itself would have been a niggardly payment, considering the fortunes that were made from his work, but the government refused to pay more than three thousand dollars.

Weir, the assistant on Markham's own travels, was turned down by the government, but the Horticultural Society voted him a life

pension of eleven dollars a month. He couldn't do very much with that sum, but he didn't want to. His South American work had left him crippled for life.

As the promoter and leader of the expeditions, Markham fared considerably better. He became Sir Clements Markham, Knight Commander of the Bath, Fellow of the Royal Society, Fellow of the Royal Geographic Society, member of scores of other scientific bodies, and holder of honorary degrees. He was a great empire builder.

While the various Markham expeditions were poking in and out of the Andes, another Englishman suddenly got excited about cinchona trees. He was Charles Ledger, an enterprising exporter, who had lived in Peru for years and who knew the cinchonas better than most botanists. In 1860 he sent his servant Manuel into the mountains to get a good crop of seeds from the best cinchona trees.

Manuel came back in 1865. He'd waited up in the mountains five years for that good crop. He brought back fourteen pounds of seed which were worth, at the most conservative estimate, one hundred million dollars.

The seeds were also worth Manuel's life, for he died soon afterward, thanks to exposure in the mountains and an indescribable session in a Bolivian jail. The Bolivians didn't like cinchona-stealers.

Charles Ledger sent the seeds to his brother George in London, and George tried to sell them to the British government. "Not interested," said the government. "We have plenty of seeds from the Markham expeditions."

So brother George offered them to the Dutch, and the Dutch bought one pound for a few dollars. That one pound was the basis of the great Dutch quinine monopoly.

The Markham seeds gave England a source of quinine, true enough, and they grew beautifully in India and Ceylon. If it hadn't been for the Ledger seeds and the Dutch industry they started, these British cinchona plantations might have cracked the South

American monopoly. But the British planters ran into trouble—insect pests, poor yields, an uncertain market—and they gave up cinchona to the Dutch in favor of the more profitable tea plants.

The Dutch planted Ledger's seeds in Java and tenaciously hung on against bugs and bonds; slowly they capitalized on the rich yields of Ledger's trees until they finally won their fight.

On their plantations on the Pengalengan plateau, these Dutch established another quinine monopoly, but unlike the earlier one in South America, theirs was a more benevolent arrangement. It still was based essentially on the theory that quinine must be reasonably cheap or it won't sell even to the one malaria victim out of every ten who can afford it. It must be cheap or another Markham or a Ledger may come along.

V

Such was the history of quinine and man's fight against malaria, a fight that started three hundred years ago. It was a history that streamed dizzily from Madrid to Lima, to London, to Paris, to the South American Andes, and to India and Java. But this part of the history, with its Chinchons and Talbor and Pelletier and Markham, stopped suddenly, and the course of the story swerved in the year 1879.

Strangely enough, until that year, malaria had been fought completely in the dark. Quinine cured malaria, but no one knew why. No one knew what caused malaria nor how it was transmitted.

Beginning in 1879, however, the world's microbe-hunters moved in. Armed with the discoveries that had already been made by Pasteur, Koch, von Behring, Roux, and the others, the bacteriologists took their microscopes and declared war against this invisible death of the tropics.

In 1879 Patrick Manson discovered that filariasis, a parasitic infection much like malaria, was spread through the bite of mosquitoes. A few months later, Laveran looked through his micro-

scope at drops of blood taken from malaria victims and found what he was looking for—a host of tiny but deadly germs which invaded and exploded helpless red blood cells.

In 1883, King accused the mosquito of spreading malaria, and immediately dozens of workers, British, Italian, and French, went to work on this new idea. Antonio Grassi snooped around mosquito-infested marshes in little Italian villages. Ronald Ross tested his hunches on every kind of mosquito and on birds and on human volunteers in India.

It took eleven years to work out all the details, but by then Ross had his story complete. He and the others had proved beyond possible doubt that malaria is caused by a germ—a strange microbe that spends part of its life in a mosquito and part in human blood. He proved that one main type of mosquito, the anopheles, is involved. He showed that quinine is effective because it destroys the malaria germ in human blood.

For this information, obtained at the cost of his own health, Ronald Ross received the Nobel prize in 1902.

With these new facts it became possible to attack malaria on new fronts, and engineers, public health officials, and sanitary experts formed a valiant army against the disease. They centered the attack against the mosquito and against its home in swamps, marshes, and stagnant pools. They fought with pick and shovel, with dynamite and oil. They wiped out literally millions of dangerous breeding places. They formed a holy alliance, these grimy, sweaty, muscled men, with the men of the laboratory, clean, quiet, and intent.

At the very time when the bacteriologists were conducting their probings in the field, the chemists were prying into the construction of quinine. In 1879 while Manson was busy tracking down the mosquito in filariasis, Skraup in Germany found one of the units of the quinine molecule, an important brick in its structure which was identified as *quinoline*. While Ross was finishing his remarkable malaria studies in India, Koenigs in Germany uncovered another quinine unit, a complex brick which he called *meroquine*.

And in 1907, five years after Ross won the Nobel prize, two Germans, Rabe and Hoerlein, discovered that the complete quinine molecule was formed by a quinoline unit and a meroquine unit, the two hooked together through a simple alcohol unit.

Here, then, were the three units of quinine—quinoline, meroquine, and the alcohol. It seemed quite obvious to German chemist Schulemann that the malaria-killing power of quinine must be a property of one of those units, but it didn't work that way. Each unit was tried by itself, then in combination, but the results were completely negative. Something was lacking.

Schulemann and his colleagues of the great German Dye Trust put their notes on quinine units into properly labeled pigeonholes and turned to a new clue. Someone had reported that a very peculiar synthetic dye, methylene blue, could kill malaria germs. Schulemann and his men wiped off their desks, put on fresh gowns, called for clean glassware, and went after methylene blue.

True enough, this blue dye killed malaria germs, but the chemists scowled. Sometimes the dye worked, sometimes it didn't. And who, even to get rid of malaria, wanted his blood pumped full of dyestuff? Unfortunately, methylene blue was too strong a dye and too weak a malaria-killer.

The chemists took out their chemical monkey wrenches and began to overhaul the methylene-blue molecule. They changed it, took it apart, removed a piece here and put another one on there, but they failed to build any vastly improved malaria remedy. At length, they went back to quinoline—one of the units of the quinine molecule—and subjected it to a similar reconstruction. Soon they found that, by attaching to it a long tail of carbon atoms, they could turn this mild chemical into a substance which was unleashed murder to malaria germs. Schulemann called this new chemical *plasmoquine.*

Unfortunately, it became apparent quite soon that plasmoquine could destroy not only malaria germs, but, unless handled with the greatest care, it could also kill human beings. "This," declared the Germans, "is not desirable."

They went back to work again and, scarcely ten years later, two other workers in the same laboratory brought forth a third new malaria-killer. This was *atabrine.*

After all their years of bad luck and apparently wasted effort, the painstaking laboratory men would not have been completely surprised if this drug, too, should kill both germ and patient. But atabrine—later to be given the official name of *quinacrine*—was infinitely more co-operative. It passed its first tests with flying colors, and then supplies were sent to hospitals, laboratories, universities, and private physicians all over the world wherever malaria was prevalent. Within a few months, the results came pouring in.

From United Fruit Company hospitals in Central America, South America, and Cuba, doctors reported the "spectacular result of curing all patients within one week or less."

From the University of the Philippines, one scientist declared that atabrine was "probably the best antimalarial drug now available."

U.S. Navy doctors working in a hospital in Nicaragua described their results as eminently satisfactory.

Physicians studying its effects on railroad workers in Bengal said the introduction of atabrine marked a definite advance in the treatment of malaria.

Similar endorsements came from a general hospital in Tennessee, a railroad hospital in Honduras, prison camps in Arkansas, and various medical groups in Greece, Panama, Natal, Ceylon, West Africa, New Guinea, and Malaya. By 1939, it appeared generally accepted that atabrine was a valuable addition to the drugs against malaria—perhaps not quite so marvelous as indicated in some early reports but certainly as good as quinine and possibly better. Although it occasionally produced a strange but temporary yellow discoloration of the skin, and although in a few people—rarely more than two in one hundred—it caused indigestion and stomach distress, more and more physicians adopted it for routine use.

Until 1939, atabrine was manufactured only in Germany. Soon after the outbreak of World War II, however, these German supplies were cut off from most of the tropics, and first English and then French colonial officers came to the United States and asked for help.

"We must have atabrine," they implored. "Can you people make it for us?"

"Why not go back to quinine?" asked an American drug manufacturer.

A British public health expert answered, "That would be going back to the Dark Ages. Atabrine is infinitely better."

Accordingly, American scientists and production engineers tackled the problem of making American atabrine. It was no easy job. They quickly learned to their discomfiture that the large-scale preparation of this drug is a long and arduous task, beset with innumerable traps for the unwary. Long before the United States entered the war, this production problem had been licked and it seemed that ample supplies of atabrine would soon be available to take care of victims in British and French colonies as well as to protect American soldiers from the menace of malaria which lay waiting in North Africa, Italy, Guadalcanal, New Guinea, Burma, and the Philippines. Then a peculiar story began spreading from hospital to hospital and from camp to camp—

"Have you heard about that lousy atabrine they're giving us? It's killed a lot of guys! A fellow I know told me . . ."

And in medical circles, one doctor would say to the next: "Maybe those Germans know how to make atabrine, but we don't. I understand that the American-made pills are dangerous."

It is difficult to discover exactly where those rumors started and on what they were based. A few self-appointed experts spoke knowingly of "preliminary, unpublished findings." Unquestionably they did start and steadily spread. It was only natural, therefore, that some soldiers vigorously refused to take atabrine pills, that more than a few medical officers declined to give them, and that finally, in the summer of 1942, the Army stopped all purchases of

the drug. The Army had official backing for its decision, for the dignified and authoritative National Research Council, discarding the early field reports as "unreliable," was on record with the decision that atabrine was too dangerous for use.

Not until 1944 did the National Research Council alter its stand. Then, faced with the unambiguous results of new studies made in a Brooklyn hospital and a New York penitentiary and with U.S. Army reports from New Guinea (a 95 per cent cut in the malaria rate in fifteen months), the Council made a complete about-face.

"In suppression of the disease, atabrine has proved to have all the antimalarial properties ascribed to quinine," its special committee decreed. "When properly administered, atabrine is fully as effective as quinine in termination of the acute attack, and is safer than quinine."

This was no great news to Army doctors or their patients in a hundred malaria-infested battle areas. Ignorant of the frightening rumors or simply ignoring them, they had used existing stores of atabrine to prevent and control and sometimes even cure malaria where this disease had run rampant for centuries. In the tropics, atabrine had saved probably more lives than bullets had taken.

During the early war years, after the complete loss of the quinine plantations in the Japanese-occupied Dutch East Indies and the temporary eclipse of atabrine, American scientists by the thousands had been mobilized by the wartime Committee on Medical Research to seek other and perhaps better substitutes. Working in industrial laboratories, universities, and both civilian and military hospitals, these men eventually tested more than fourteen thousand substances.

"Never before," declared one health official, "have scientists launched such an intensive attack against a disease."

They tested new chemicals which they themselves created. They also tested existing chemicals, fertilizers, plasticizers, nylon

intermediates, rubber accelerators, Chinese herbs, mud from the River Nile, the lower leaves of the cotton plant, and eggshells suspended in choice whiskey.

"We got some of these things as suggestions sent along by well-meaning folks who were convinced they had the answer," one researcher explained. "It was easier to test them than to write a convincing letter explaining why they wouldn't work."

Any potential drug which seemed to possess even the faintest glimmer of value was tested on chickens, canaries, ducks, turkeys, monkeys, and finally human beings. Many a conscientious objector to military service risked his life for his principles by taking, first, a shot of virulent malaria microbes and then some brand-new chemical which might kill them—or him. Many a prisoner in a penitentiary paid part of his debt to society by volunteering to take large doses of a new and relatively untested drug, day after day for months at a time, so that doctors might discover its danger to human tissues.

Of the thousands of compounds brought in for test, scarcely one in ten had the slightest merit and only eighty out of the entire batch seemed to be good enough to try on humans. And, strangely, the scientists came upon some of the best of these by following clues which their German colleagues had kindly left for them.

In 1939 the Germans had taken out patents on twenty-two new synthetic chemicals as potential antimalarials. This was not a world-shaking phenomenon, for the Germans were always patenting new cures—most of them worthless. A few years later, these patents were extended to the Winthrop Chemical Company for the United States. There was nothing secret about any of this; the patents were published, the formulas were published, and any one was free to investigate them.

"That's where the Germans fooled us," an American said later.

Of these twenty-two drugs, the Germans selected one they called *sontoquine* as the best. Promptly the Winthrop chemists in New York prepared some of this sontoquine and offered it to the Com-

mittee on Medical Research for trials, but nobody seemed to be particularly impressed, and sontoquine—along with the other twenty-one new German chemicals—was forgotten.

In 1943 American troops in North Africa captured some Nazi prisoners and found them to be carrying vials of pills which the Germans freely admitted were to be taken for malaria.

What were these pills? No one appeared to know. They were white and tasteless, and therefore could not be either atabrine, which is yellow, or quinine, which is bitter. Immediately they were rushed to America under the highest priority and then turned over to American scientists for analysis.

"Get going on these right away," the scientists were told. "And when you find the formula, don't whisper a word about it. We don't want the Nazis to know we've got it!"

The Nazis would not have been surprised at all. Laboratory studies revealed that the white, tasteless pills were composed of sontoquine.

Now, with their faces quite red, the Americans hurried to re-examine sontoquine. They also examined the other twenty-one chemicals in that 1939 German patent list, and found that the Germans had committed an even more embarrassing blunder—there were at least three other chemicals in that list which were vastly superior to sontoquine, three others which the German investigators had apparently discarded after only superficial tests.

It took many months of studying these drugs, testing them first on birds, then on monkeys, next on prisoner volunteers at Atlanta, Joliet, and Rahway, and finally on selected groups of soldiers, before their value became apparent. From these trials and from later studies on infected school children and adults in India and Burma, malaria experts concluded that the new compounds—*chloroquine, oxychloroquine,* and *pentaquine*—ranked among the best malaria remedies ever found.

The first two, chloroquine and oxychloroquine, appeared to be much better than quinine—even better than atabrine!

Soon British workers developed still another drug, *paludrine,*

tried it in England and Australia, and announced, "It is undoubtedly the most potent antimalarial drug known. Its discovery is a triumph for British chemotherapy."

The field trials on all these new compounds were so long that it was late in 1946 before the first of them was put in commercial production, and by that time, still newer and perhaps better synthetic antimalarials had been created and were undergoing trials. Whatever the final decision in all those trials might be, one fact stood clear: no longer need millions of malaria victims be totally dependent on forests or plantations of cinchona trees. Now the weapons against this old disease could be forged in the laboratory.

CHAPTER III

Housewife's Recipe

WITHERING AND DIGITALIS

For a thousand centuries, men have suffered from a widespread malady that puffed their bodies into grotesque shapes, squeezed their lungs, and finally brought slow but inexorable death.

Steadily, as the disease progressed, a watery liquid filtered into every available space and expanded it like a balloon. Sometimes the liquid—quarts or even gallons of it—made arms and legs swell so they were immovable. Sometimes it poured into the abdomen to form a tremendous paunch. Sometimes it waterlogged the lung cavity and thereby made it impossible for the victim to breathe unless he sat bolt upright all day and all night.

This watery sickness was *hydrops* or, more commonly, *dropsy*. After tuberculosis and the other infectious diseases, it was one of the chief causes of death. It was so ten thousand years ago, a thousand years ago, even a century ago, and, but for an almost miraculous green leaf, it might be the same today.

Throughout western Europe, botanists were well acquainted with the tall, heavy-leaved plant with the bell-shaped blossoms which today is called foxglove.

In the middle ages it had a dozen names. In early England it was called "foxes' glew" or "foxes' music." The Scotch knew it as "bloody fingers" or sometimes as "dead men's bells." The Norwegians called it "foxes' bells." In France it was "Our Lady's gloves" or "Virgin's fingers." The Germans called it "finger-hood" or

"thimble," and with this name in mind the old Latinizing herbalists officially dubbed the plant *digitalis.*

One of these old botanists, a Bavarian physician named Leonhard Fuchs, who worked four hundred years ago, did more than list the plant and describe its flowers, seeds, leaves, stem, roots, and habitat. Convinced it had truly wondrous powers, he also pointed out its uses to physicians: to scatter the dropsy, to relieve swelling of the liver, and even to bring on menstrual flow.

But this earnest observer was passed off as a mere flower-picker, though he actually knew a great deal about medicine, and the good physicians of his day paid very little attention to him. They didn't pay much attention, either, to others who claimed that foxglove, or digitalis, could "scatter the dropsy"—men like Gerrarde, who used it as an emetic, and the Dutch medical botanist, Dodoens, who wrote that "for those who have water in the belly . . . it draws off the watery fluid, purifies the choleric fluid, and opens the obstruction."

The plant scientists failed to understand why their medical colleagues remained so aloof. Anyone with half an eye could see it was being used by illiterate farmers and housewives in England and on the continent. These folk, who knew nothing about medicine, still knew enough to use concoctions of digitalis for dropsy. But not the doctors!

After being impolitely kicked about for centuries, digitalis finally broke into good medical circles. In the year 1722 it was admitted into the great London Pharmacopoeia, the "Who's Who" of acceptable drugs; a few years later, it was in the pharmacopoeias of Edinburgh, Württemberg, and Paris. Its acceptance was due primarily to a glowing testimonial provided by the English herbalist, William Salmon.

"Foxglove," described this eminent scientist, "is hot and dry, at least in the Second Degree, Sulphureous and Saline, Aperitive, Abstersive, Astringent, Digestive and Vulnerary, Pectoral, Hepatick, and Arthritick, Emetick, Cathartick and Analeptick. . . .

"It cures Consumption," he said, "but it should be used with great Caution because it produces Weakness, induces Vomiting and purges; it cleans the Body from Top to Bottom and thereby rids it of tenacious Humours."

Even with the caution required, who could resist such a eulogy? But there was even more.

"This medicine," Salmon continued, "has restored (where the patient has not been past cure) beyond all Expectation. It cures a Phthisick or Ulceration of the Lungs, when all other medicines have failed and the Sick esteemed past Cure. It opens the Brest and Lungs, frees them from tough Flegm, cleanses the Ulcer, and heals it, when all other Remedies act without effect.

"I have known it to do Wonders, and speak here from a long Experience. Persons in deep Consumptions, and given over by all Physicians, have been strangely recovered as to grow fat again. I commend it as a Secret, and it ought to be kept a Treasure. These few lines concerning this Medicament alone are worth ten times the Price of the whole Book. . . .

"I am very confident of it, the deplorable wasted Patients . . . if they make use hereof, will give me Thanks for this Notice, whilst they may have Reason enough to Curse even the Memories of Quacking Bloodsuckers, Issue-makers and Blister-drawers, who, as they may have drained them of a fair part of their Estate and Treasures, would, by a continuance under their hands (for all their specious Methods of Cure), have been fooll'd out of their lives too. . . ."

So spoke William Salmon, herbalist. Of course, he was slightly overenthusiastic and considerably in error. Digitalis did not produce the miraculous effects he described, nor did it cure tuberculosis (his Phthisis or Consumption). But no one knew that at the time or for many years to come, since it was often difficult to distinguish between tuberculosis, which digitalis will not cure, and dropsy of the chest, which digitalis relieves quickly. That mix-up between tuberculosis and dropsy was destined to cause plenty of confusion through the next two hundred years.

Thanks to Salmon's fervent exhortations, digitalis was given recognition for a time. Doctors who once had overlooked the plant were now making decoctions and extracts of the leaves, the flowers, the seeds, and the roots and giving them to their patients. Not all doctors were so inclined, however; many still saw no good in the plant.

Then, in the city of Orleans, half a day's ride to the south of Paris, a French scientist walked out of a poultry yard and completely ruined what reputation digitalis had.

Behind him, Dr. Salerne had left a pair of dead turkeys—dried, wizened, scrawny birds, which looked as if they had been squeezed like a sponge. Two weeks before, he had heard that a turkey died after an accidental meal of digitalis leaves. Now he had tried the experiment under his own observation; he had forced digitalis leaves down the throats of healthy turkeys until they could take no more. Within four hours, the turkeys seemed so drunk they could hardly stand. In a few days, after more digitalis had been fed the poor birds, they sloughed off weight in chunks. After they died, they were cut open. Their insides were as dry as if they had been baked; heart, lungs, liver, stomach, and gall bladder were shriveled and desiccated.

Salerne had proved that an overdose of digitalis is poisonous, but this French doctor went too far and assumed that any dose of digitalis is deadly.

This alarming report was sent to Paris and read before the Academy of Sciences. The news spread from there to all the big cities of Europe. Within a few years digitalis was "lost" again and disappeared from the pharmacopoeias. No doctor worthy of the name cared to use a drug that killed so horribly!

With digitalis back on the black list, the many doctors who had never approved it now went about smirking, "I told you so!" But the peasants, the farmers, and the old wives paid no attention to the men of letters. They had used digitalis long before it was listed in the pharmacopoeias, and they continued to use it long after it was banned. French turkeys, dead or alive, meant nothing to them.

II

In 1741, in the midst of all this confused hullabaloo about dropsy, tuberculosis, digitalis, and dead turkeys, William Withering was born in the Shropshire village of Wellington, a few miles from Birmingham.

It was inconceivable that he should be anything but a doctor: selection of another profession would undoubtedly have brought down the wrath of Hippocrates. His father was a doctor, his two uncles were doctors, and even his grandfather had been a doctor, the very obstetrician who had delivered the great Samuel Johnson.

After a preliminary education from a near-by clergyman, who found him neither particularly stupid nor particularly bright, young Withering went off to medical school in Edinburgh. There he fell under the influence of some of the greatest teachers in all Europe—the chemist, Joseph Black; the anatomist, Alexander Munro; the neurologist, Robert Whytt; and William Cullen, onetime barber, apothecary, ship's surgeon, and now professor of the practice of medicine and, incidentally, the first British medical professor to discard Latin and give his lectures in English.

There was also Dr. John Hope, the distinguished professor of botany. Withering, however, did not like botany. Medicine, surgery, anatomy, chemistry—these had color, excitement, and practical application, but botany . . .

"The botanical professor," he wrote his father, "gives annually a gold medal to such of his pupils as are most industrious in that branch of science. An incitement of this kind is often productive of the greatest emulation in young minds, though, I confess, it will hardly have charm enough to banish the disagreeable ideas I have formed of the study of botany!"

At the age of twenty-three, this was William Withering, who was destined to become one of the greatest medical botanists of all times.

Two years later he graduated from Edinburgh, wrote a thesis on "Malignant Putrid Sore Throat," and was given a graduation

present of the usual fashionable tour on the continent. The tour ended prematurely with the death of his delicate young traveling companion from tuberculosis, and Withering came home looking for a place to set up practice. He decided on the town of Stafford.

It was a good choice. Stafford was near enough Wellington that the prestige of his father and uncles would help in establishing his own reputation. Furthermore, an old Stafford physician had just died, leaving a vacancy in the town's medical circles. And, of most importance, young Withering had recently cured a prominent citizen of Stafford; so he already had a patient.

Additional business, however, was harder to get. The town seemed alarmingly healthy, and the few who did get sick either had no money or went to another doctor. There was one patient, though, who seemed to require Withering's full attention. She was Helena Cooke, much more beautiful than ill, who was favored by almost daily visits from her young physician. During her long convalescence, she indulged in the charming occupation of flower painting. Nothing would do but that Dr. Withering must bring flowers on each visit—different flowers that had to be plucked from field and meadow and hedge and streambank.

Thus, spurred on by love, Withering reversed his earlier philosophy and became an earnest flower-picker. He learned to identify these flowers in order to speak fluently to his patient. He learned where they grew, when they grew, and how they grew. He was on the road to becoming, of all things, a professional botanist.

Fortunately his practice gave him plenty of opportunity for such extracurricular activities. Patients were still scarce, and he had plenty of time to study flowers, perform on the flute and the bagpipe, and take part in the local Shakespeare Club productions.

After a five-year courtship, Withering and the flower-loving Miss Cooke were finally married. Marriage brought the doctor to the sad realization that his practice in Stafford could hardly be called extensive or even profitable. A move was clearly indicated, but Withering had to wait three years before the proper opening could be found.

Meanwhile, in the midst of this idyllic though unprofitable life, medical history suddenly offered him a place among her heroes. The offer came from a very ordinary patient who requested advice on an old family prescription.

"This isn't my recipe," she said, "but I'm so anxious to have your opinion on it, doctor."

"Ah," smiled young Dr. Withering, "please allow me to examine it." He looked at the scribble, read a long list of herbs, and scratched his wig very professionally. "Interesting, most interesting! And what is it for, may I inquire?"

His patient fidgeted in embarrassment. "Well, now, doctor, I realize it may be perfectly useless. It's not my own recipe at all. I came on it by accident, like. It's just an old family remedy here in Shropshire. They use it all through the country to cure the dropsy."

"Dropsy?" Dr. Withering repeated reproachfully. "My dear lady, there is, unfortunately, no cure for dropsy. Unhappily, we of the medical profession know it to be an incurable affliction. This recipe . . . well, if you'll pardon me, you know we see so many of these local superstitions."

"Oh, doctor, is it just a superstition? But, to be sure, you must know best. Yet it has surprised us to see these herbs cure so many dropsies after the physicians have given them up."

Withering's face still wore its tolerant professional smile; then suddenly he sobered. "So? Actually cured the dropsies? You don't say! Most amazing and yet . . . ah, if I may see the list again. . . ." Muttering as he checked off each plant, he now carefully read the ingredients, "Primrose leaves. Hmm-mm, no good. Roots of the pondweed. That wouldn't work. Ribwort, that's inactive. Wintergreen, that's just for flavoring. Hornwort. Waxberries. No chance. Ah, wait, what's this—foxglove? By Jove, could that be it?" He turned to his waiting patient. "You're quite certain, of course, that this formula has cured the dropsy. You've actually seen it?"

"Yes, indeed, doctor, we've all seen it. Everyone in Shropshire knows it can cure!"

Withering sniffed. "Of course, dear lady, of course. You've all seen it. Very impressive, I'm sure. And now as to my opinion. I should say—but unprofessionally, mind you!—that this recipe is possibly an excellent cure for the dropsy, but I should like to try it myself. I shall let you know immediately. So thank you, my dear lady, and good-by. Good-by, good-by, good-by. . . ."

Withering closed the door and sat down at his desk. Foxglove, he thought, that's what it must be. Foxglove, good old digitalis. It couldn't be anything else. Same plant family as nicotine and belladonna. Must be active on the body. That's what cures the dropsy—if the dropsy is cured. Lord, I'll have to have a try at it. Wonder what would happen if I gave some to old Nichols. He's full of water, dying from it. How much ought I to give now, and how . . .

Few paying patients came to see Dr. Withering, but there were dozens of others, the "sick poor," who couldn't pay. They were treated without charge, and on those of them who suffered from dropsy, Withering decided to try digitalis.

And how that digitalis did work! He used a few doses of the leaves steeped in water or just powdered, and the liquid flushed out of some patients like a cloudburst. Pouring from the kidneys in gallons, it drained swollen chests and bellies. It wiped out every sign of the dropsy like a magic eraser. But, unfortunately, it was a suprisingly erratic cure.

Dr. Withering didn't know how to prescribe digitalis. Should he give a grain, an ounce, a pound? Should he give it hot, or should he give it cold? Should he give it once a day, twice, or thrice? Should it be given before or after meals, should it be given daily, should it be continued for days and days?

Nobody could answer those questions, for digitalis leaves didn't grow in nature with the directions printed on them. Withering had to experiment, and the experiments didn't make sense. Old Nichols had to take only a few grains before the water surged out; whereas poor Dame Twombley needed twice as much. And young Smith didn't lose water at all; he just grew terribly sick.

That digitalis sickness was frightening, too. Sometimes it was

mild, but more often it meant violent nausea, vomiting, purging, headache, spots before the eyes, and a host of other alarming symptoms.

The patients didn't like that part, either. Around the village they complained, "That young Dr. Withering nigh killed my poor man." . . . "He give me some an' I come that close to dying!" . . . "As for me, I'll keep my dropsy, and he can keep his medicine!"

Withering was thoroughly upset. Digitalis worked; there was no question of that; but how it worked! He wanted to cure those poor swollen devils, but he had taken his oath—he couldn't risk a human life. True, digitalis hadn't killed anyone yet, but with this hit or miss, well . . .

At night he talked to Helena about it, told her his hopes and fears. She was sympathetic and, under the circumstances, very wise. "Leave it alone, William, leave it alone," she counseled. "They got along all right without the digitalis before. Don't risk spoiling your life by killing someone with it. Wait for a while, William, and think about it."

William waited and thought. Finally he had almost convinced himself that digitalis was more dangerous than it might be useful and that, furthermore, it had only helped a few of his "sick poor," nobody important, really.

Then, while digitalis faded further and further into the background of his mind and he was again face to face with the inadequacy of his income, a letter arrived.

"Dear Doctor," he read, "I am at this moment returned from a melancholy scene, the death of a friend, Dr. Small of Birmingham. . . . I saw by the papers he had gained about five hundred pounds a year from his practice. A person at Birmingham desired I would acquaint you with this. . . . If you should think this prospect worth going into. . ."

Withering dashed to find his wife and thrust the letter in front of her. "Look, Helena, an opening in Birmingham! It pays five hundred pounds a year. Do you hear that? Five hundred pounds! It's a fortune!"

Helena tried vainly to see the paper he was waving in the air. "William, wait. A letter—who sent it?"

"Who? I don't know. Fellow by the name of Erasmus Darwin. Never heard of him, but hurray for the old boy!"

So William, his little daughter, and Helena, heavy again with child, moved across the county line into Birmingham. Thanks to Erasmus Darwin, brilliant physician, naturalist, grandfather of the immortal Charles Robert Darwin, and thanks to a few other men who had admired Withering's work in Stafford, the thirty-three-year-old physician began a new and glittering chapter of life.

It was 1775, and Birmingham was already becoming the bustling, crowded, dirty English city that one day would be second in size only to London. Factories were running at top speed, trade was booming, and the whole world was calling for Birmingham buckles, buttons, metalwork, toys, and guns. There was peace throughout the world (except for a silly little fuss with the American Colonies), and life was excellent.

For Withering there was a splendid medical practice, an appointment as junior physician to the Birmingham General Hospital, and important friends whose names were known all over the world. His predecessor, the lamented Dr. Small, had been popular in the city, and Withering was given every chance to fill his place.

Patients streamed into his consultation room—paying patients. His income began to soar. He had less and less time for his hobbies now, but he made them more productive. His amateurish interest in natural history had developed into a professional knowledge of mineralogy. His early dislike of botany had been completely forgotten, and he published a monumental book—*A Botanical Arrangement of all the Vegetables Naturally Growing in Great Britain.*

The first complete English handbook of all plants in the British Isles, it was to be the outstanding botany book for half a century. It helped start a vogue for flower-collecting which was the equal of the more modern fads for stamp-collecting, amateur photography, or plane-modeling.

It was perfectly natural, too, that these amateur botanists should call in a man like Withering, who could examine both their blossom collections and their livers.

The popular doctor was soon put up for Birmingham's unofficial brain trust, the Lunar Society, and welcomed into membership. The Society had a magnificent lot of members—Jamie Watt with his infernal steam gadget and wild William Murdoch, who proposed to light cities with gas; Matthew Boulton, inventor, capitalist, and Watt's patron; Josiah Wedgwood, the pottery man; Joseph Priestley, the chemist who discovered oxygen; and the astronomer, William Herschel. There was a quiet Quaker, Benjamin Franklin, who was welcomed even though he had connections with the rebel government in America. Dr. Erasmus Darwin was also a member of the Lunar group and a real friend to Withering, whose practice he constantly helped to enlarge.

At the hospital where Withering's appointment brought him more experience and training, he found another friend in his chief, Dr. John Ash. One day Dr. Ash asked him about digitalis. "You used the leaves for dropsy, didn't you?"

"Oh, yes," Withering answered, "but that was quite a while ago. I had to give it up. Seemed pretty dangerous and rather frightened my patients. Why do you ask?"

"No reason. Just curious. Don't happen to have any notes on your results, do you?"

"Umm, no, sir, I never took any. You know how it is. I just used digitalis on my sick poor, and I was so rushed with them, twenty in an hour sometimes, that I didn't have time to take notes."

Ash sighed, "Most unfortunate. I would have liked to check on this. You might glance at it, in any case."

He passed over a letter which Withering read quickly. "Lord, what won't those quacks do next!" he exclaimed. "Imagine one of those fellows curing a dropsy with digitalis after all the physicians gave him up for dead!"

"Rather," Ash agreed, "and look who the patient was—the famous Dr. Cawley, himself, head of Brazen Nose College at Ox-

ford. You'd think a man with his standing would know enough to stay away from those untrained practitioners. Ah, Withering, you don't suppose, do you, that it might be wise to try digitalis again?"

Withering stood up. "Most strange of you to ask that, sir. I was just about to make the same suggestion myself."

Back to digitalis. Back to the bright green leaves, to the swollen patients, to the nausea and the vomiting and the miraculous outgushing of water through the kidneys. Back to the fears and the worry and the unco-operative patients.

There was one point in the case of the Brazen Nose principal, however, that was particularly upsetting. Withering discovered that the esteemed Dr. Cawley had taken a terrific dose of digitalis, twelve times as much as anyone his size could be expected to stand, and yet he had stood it and was cured!

Back home, Withering fretted at that impossibility. It made absolutely no sense at all unless . . . unless digitalis wasn't as dangerous as he feared, unless he had been worrying himself needlessly. He walked out of his study and called to his wife. "Oh, Helena, I thought you might be interested. I'm going to try our digitalis again."

Helena lifted her eyes to the ceiling and whispered, "Dear God, again. . . ."

III

Withering was wrong, dead wrong. Digitalis could be terribly dangerous and even fatal. But, for a little while at least, he forgot that and went back to work with freshened confidence. There were plenty of dropsical patients who would do anything that the now famous doctor advised, and there was plenty of digitalis.

It took years before Withering realized he had bumped into the trickiest dosage problem in all medicine. There was no standard dosage for digitalis! Good Dr. Cawley of Oxford had survived a huge dose because he was just that kind of man, while others could stand only the tiniest amounts. Withering learned, by the long,

hard way of trying, that each dropsical patient had his own particular limit.

How could that limit be discovered? Withering slowly worked out the answer and explained it to his fellow members at the Lunar Society meetings. "You see," he said, "I begin on each patient with a very small dose. Finally I reach an amount that brings action, a dose that produces vomiting and purging and slows down the heartbeat. That's the dose I've been looking for in that particular patient. I know that's his limit. All I have to do, then, is give him just a bit less than that limit, and he's happy. Furthermore he gets over his dropsy!"

The Lunarites were properly impressed. "By God," Jamie Watt roared, "it's uncanny the way you medicos get onto a thing like that!"

But Birmingham doctors were a little more aloof. They were inclined to believe Withering, but where was his proof? Withering had abundant proof. He knew now the mistakes of his first trials at Stafford—he'd given too much digitalis or too little, and he'd given it for too long. Now he was more cautious; now he was curing his patients—not many, at first, for he started very carefully, but he was curing them. Moreover, he now kept records.

Dr. Erasmus Darwin, one of the most stubborn opponents, remained unconvinced until Withering used digitalis to save a patient whom Darwin himself had given up.

In 1775, his first year in Birmingham, Withering jotted down in his book: *1 case tried; 1 case cured.*

In 1776 he wrote: *4 cases tried; 4 cases cured.* (In that year he noted, too, a peculiar, bothersome cough that was making him irritable and a tendency to be unusually tired at the end of the day.)

In 1777 he wrote: *8 cases tried; 2 cured, 2 relieved, 4 failed.* (Consciously he had tried to use digitalis to cure tuberculosis as well as dropsy, and scrupulously he reported his failures.)

In 1778 he wrote: *5 cases tried; 1 cured, 1 relieved, 3 failed.* (He

was still stubbornly trying to cure tuberculosis along with dropsy.)

In 1779 he selected his patients more carefully: *6 cases tried; 5 cured, 1 relieved.*

Withering was not yet sure enough of his ground to make a report in writing, but he let a friend carry a message to the imposing Edinburgh Medical Society. The entranced Scotch doctors listened to the new miracles of digitalis. They hailed the Birmingham physician and immediately made plans to restore digitalis to the Edinburgh pharmacopoeia. "Why," they puzzled, "did we ever throw it out in the first place?"

News of the dropsy cure now began to spread, and details of the treatment were passed all over Scotland and England by word of mouth. More and more patients were given the drug, and their swollen, fluid-filled bodies deflated to normal size.

Then, without the least warning, Withering learned that another doctor was trying to claim the discovery for himself. It was the very man who had brought him to Birmingham and given him unceasing help. It was, indeed, the eminent Dr. Erasmus Darwin.

It seemed completely unthinkable, but the facts were there. Darwin's son Charles, a medical student at Edinburgh, had died two years before at the age of twenty. He left a dissertation on dropsy, and after his death, his father decided to publish it. In an appendix to this book Erasmus included reports on nine cases of dropsy all cured by digitalis. Withering's name was not even mentioned.

Withering was horrified. This little pamphlet, the work of the two Darwins, contained the first written proof that his digitalis would cure dropsy. More shocking yet was the fact that the first case listed was the patient who had been given up by Darwin and saved by Withering.

The entire medical profession of Birmingham was rocked, even below its foundations. All the local men knew that Withering had done the work, and now one of their own colleagues had claimed credit for the discovery—claimed it in writing before the world.

Of course nothing could be done. It would have been most unseemly for Withering to seek a duel or demand an apology or even to shout "thief."

For months he was crushed by the knavery of his trusted friend. Accumulating more and more data on his patients, he quietly kept at his work. In the meantime he continued his investigations in mineralogy and general botany. His bothersome cough had become more serious; soon he diagnosed it himself as tuberculosis.

Each year now he was growing weaker. Still in his early forties, he had to give up his medical practice for long months at a time. In 1785 when he was forty-four and had spent ten full years on his digitalis studies, he decided the time had come to publish his conclusions.

It was high time that this be done. Many doctors were disregarding his advice and using digitalis for tuberculosis, scrofula (the king's evil), and a host of other diseases. He knew that in these maladies it was absolutely worthless. Other doctors, in treating dropsy, were administering the drug sloppily, paying no attention to the vital necessity of determining the proper dose for each individual.

Withering's book was published under the title of *An Account of the Foxglove, and Some of Its Medical Uses, with Practical Remarks on Dropsy, and Other Diseases.*

One of the milestones of medical progress, it announced one of the greatest discoveries of all times. It was reprinted, translated, and spread throughout the world.

Publication brought the highest honors to Withering—a fellowship in the Royal Society, a diploma from the London Medical Society, a fellowship in the Linnaean Society. It made him one of the wealthiest and most prominent physicians in England.

But the honors could not stop the slow march of the tubercle germs. For eleven years more he continued his work with increasing pain and weariness and was finally forced to retire in 1796 at the age of fifty-five. He died three years later.

In the year of his death almost every important medical journal

carried glowing reports on the use of digitalis in curing—not dropsy—but *tuberculosis.* The medical world had completely missed the point. . . .

IV

It was amazing how the medical giants back in 1800 ignored the meat of Withering's discovery and gulped down the indigestible scraps. Withering knew, so very surely, just what digitalis could and could not do. He asserted in unmistakable words that he had found digitalis worthless in tuberculosis. He proclaimed with vigor that digitalis "has a power over the motion of the heart to a degree yet unobserved in any other medicine."

But the bungling practitioners believed only what they wanted to believe. They wanted a cure for tuberculosis, and for twenty years they scraped and bowed before digitalis as that cure. They beamed happily as they deluded themselves by saying, "Consumption will henceforward be cured as regularly by the foxglove as malaria by the Peruvian bark!"

It was an unbelievably exasperating, pathetic, and thoroughly stupid situation. It saved the life of not one tuberculous victim.

Digitalis was also being miserably mishandled by even those men who were using it for dropsy. Withering had explained how the treatment should be given, but he was dead, and nobody remembered or bothered to read his directions again.

On the one hand, there were men like Hahnemann, the founder of homeopathy, who tossed off Withering's book with the retort that "inasmuch as digitalis also produces headaches, dizziness, and such, its usefulness seems very limited." There were great heroes of medicine like Laënnec, discoverer of the stethoscope, and Corvisart, physician to Napoleon, who refused to admit that the drug could even cure dropsies.

And on the other hand, there were men who were certain that digitalis should cure every case of dropsy and who were very

annoyed when it didn't and consequently pumped tremendous overdoses into their gagging, rebellious patients.

Thirty years after Withering's death, digitalis was sliding back to oblivion again, sliding on the grease of petty jealousies, unscientific handling, and sheer ignorance. They were getting ready to read its funeral service: "It should have cured tuberculosis, but it didn't."

Then, like a band of avenging wraiths, a new army moved to the rescue. They were no rich, dignified, important doctors. Out of the world's great laboratories and clinics they came armed with scientific evidence—pages of it, books of it, crates of it. Slowly they built their scientific forts and armed them with scientific weapons. Cautiously they moved to the attack. They were painfully, exasperatingly slow, but they could not be stopped. They gathered the facts, and the facts could not be questioned.

Does digitalis cure tuberculosis? "Look at your own results!" they thundered. "You, yourselves, have treated a thousand consumptive patients with digitalis, and what happened? All thousand died—of consumption."

Is digitalis too dangerous to treat dropsy? "Not when it is used properly," they emphasized. "Not when you use the proper dosage for each individual patient, as Withering himself told you."

These scientific men and the host of others who soon joined them seemed to have all the answers. Looking for the active principle, they probed into the digitalis leaves just as Sertuerner had done with opium and Pelletier and Caventou with cinchona, and came out with potent white crystals that did everything that crude digitalis could do.

This active principle was discovered first in France by Nativelle, the year before the Franco-Prussian War, and labeled *digitalin.* It was "rediscovered" a few years later in Germany by the great Schmiedeberg, who, possibly a trifle excited by wartime hysteria, forgot about digitalin and named the German product *digitoxin.* It was no alkaloid, like morphine or quinine, but apparently a completely baffling complex consisting, in part, of a sugar.

Gradually this war between clinical practicalities and scientific exactitude took on a new appearance. The old, tuberculosis-curing, overdosing physicians had gone, and a new generation of doctors was starting to practice.

"Very well," these young men agreed, "you've proved that digitalis won't cure tuberculosis or anything else but dropsy. We have no argument with you. But tell us, just *how* does digitalis work? What does it do to the heart? Why do our patients get dropsy? What has the heart to do with that? Why doesn't digitalis cure all our dropsical patients?"

"Your patients?" the laboratorians shrugged. "We don't know anything about your patients. But just look what we've found out about the chemical constitution of digitalis!"

The doctors were dismayed. They didn't care about chemistry; they wanted to cure patients. The scientific men didn't care much about patients; they were too absorbed in their rats and frogs and test tubes.

There was a crying need for great men to clarify the situation, and soon three of them marched into battle.

First there was Arthur Cushny, who had gone from Scotland to teach drug-science at the University of Michigan and later at the University of London. He knew how to use digitalis in the laboratory, but he also realized that medicine's job was to cure men and not frogs.

Second there was good Dr. Wenckebach, who had been an obscure family physician in Holland and then secured a job as doctor in an old folks' home. (And where could there be a better place to listen to sick hearts?)

And finally there was the "beloved physician," the Scotch James Mackenzie, who was most proud of his ability as a family doctor and just a bit displeased when the world later called him the greatest living "heart specialist." He knew the practice of medicine. He had done his own diagnosis, his own treatment, his own surgery, his own midwifery, and his own anesthetizing, and he had really studied hearts.

Dropsy, these men found, resulted from a strange sickness that attacked the muscles of the upper heart—a sickness that changed the slow, powerful, regular pumping into a weak, flabby, uneven squirting. There was no power in this "delirious heart." It didn't push the blood along fast enough, but allowed it to lag and swell out veins and drown the tissues.

This sickness, which doctors now call "auricular fibrillation," totally wrecked blood circulation. It resulted in stagnation, in great accumulations of blood in the big blood vessels, from which watery fluid filtered out to swell arms, legs, chest, and belly.

These men learned that digitalis halted that flabby, weak, deadly tremor and made the heart go to work again, pumping the blood with good, hard thrusts. This revitalized blood circulation, like an automatic delivery truck, picked up the fluid in the swollen tissues and carted it off to the kidneys to be flushed out of the body.

They proved that in this type of heart disease, digitalis could bring comfort and relief and that it could magically forestall impending death. But digitalis could do this only when administered properly and not in the way its administration was being bungled by most physicians.

There was the story. It wasn't complete in every detail; it still isn't, even today; but it had all the main ingredients. Its preliminary announcement, however, fell on deaf ears. It wasn't that the Important Doctors didn't believe it; they were much more insulting—they disregarded it.

After all, who was Mackenzie? Merely a pleasant general practitioner. Who was Cushny? "Oh, Cushny, he's that wild man who picked up strange notions over in America." And Wenckebach? A Dutch country boy with a lot of fairy tales!

Finally in 1910, Mackenzie himself brought the fight right to Harley Street, to the very center of rock-ribbed conservatism. He set himself up in practice and began to show the Harley Street specialists that they were actually letting their patients die by refusing to treat them properly. In a remarkably short time Mackenzie won recognition but not in the way he had hoped.

Many years before, he had invented a couple of ingenious pieces of apparatus, handy gadgets to help him study bad hearts. In Harley Street the important specialists saw these gadgets and exclaimed, "Heavens! Here is a great man, an important inventor, even if he is a country practitioner. Let's elect him to the College of Physicians. Let's see that he gets some nice honors and a batch of hospital appointments."

Mackenzie got the honors, including a knighthood. But Sir James Mackenzie was still the same old Doc Mackenzie who didn't like to see patients die because of old-fogy notions. He was thoroughly wretched that he had been acclaimed, not because he had found out how to treat heart disease with digitalis, but because he had invented a few mechanical gadgets.

The Harley Street men couldn't get the point. They shook their heads, shrugged their shoulders, gave Mackenzie more honors, and insisted on showing him off to visiting foreigners.

It was years before the important new ideas took hold, before digitalis assumed its rightful place in the medical war chest. Cushny and Mackenzie died, and Wenckebach retired from active practice, but they all left students who became eloquent and convincing disciples. Today, thanks to the work of these men, modern doctors know what digitalis can do and what it can't. These men completed the first great victory over heart disease, and they also taught drug-hunters another fundamental lesson—*The value of a drug is determined, in part, by the brain of the man who administers it.*

During those years when scientists were attempting to fight superstition and ignorance with facts, there were times when doctors almost believed that digitalis was the only drug for the heart. If digitalis brought no relief, they felt, then the patient was surely doomed.

But medical memories had temporarily lapsed. For centuries doctors had not known about digitalis, and yet they had treated dropsy. They had used squill, the fat bulb of the Mediterranean

sea onion (it's amazing that they ever happened to try it!), and they had cured patients. Even today, squill is used to cure some dropsical patients, some bad hearts that digitalis can't help. They also used a concoction made from the leaves and the branches of the flowering oleander, another age-old prescription which likewise strengthened the heart.

Then in the middle of the nineteenth century, when practical physicians sniffed at the high-browed science of laboratory workers, a whole battery of new drugs came to fight against heart deaths.

These same laboratory men, lost in the clouds of research and given up as hopeless by their more pragmatic brothers, had not been wasting their time. Even though their experiments had not been of much help to waterlogged patients, their animals and their test tubes had turned up some remarkable clues. Of course these discoveries weren't labeled "clues"; they consisted of an odd bit of information here and another there and a third which tied in with the others. Month by month, as the laboratory men pooled their findings, the jigsaw puzzle was being completed.

"Look here," they said, "digitalis cures dropsy by doing thus and so to the heart. So does squill. So does oleander. Now, isn't it interesting that the active principles of these three unrelated plants are all alike chemically and all act alike on our experimental animals?

"Maybe this is significant. Maybe we've unearthed a whole new family of chemicals. Maybe if we look further we can find more of them, other members of this family which can also cure bad hearts."

But where could they look? These new chemicals weren't monopolized by any particular section of the plant kingdom, and testing thousands upon thousands of plants just on the faint hope that one or two might have heart drugs was surely out of the question. A search like that would have been impossible, but suddenly it appeared that it was also unnecessary—it had already been made over a period of centuries by thoroughly unscientific savage tribes.

One day in a Russian laboratory, two scientists examined a crude plant extract from the island of Madagascar. It was a powerful extract, a deadly poison made from the fruit kernels of the Tanghinia tree. In Madagascar the natives used it as an ordeal poison, a chemical jury. "If you eat this and die," the natives said, "then you are guilty!" It was remarkable how many thousands during those years were guilty. . . .

The Russians toyed with Tanghinia extract. It was an interesting poison, but only that—at first. They tried it on their laboratory animals and watched the poor beasts slowly stiffen and die. It was only after they autopsied the animals that they saw the light, and then they rushed off a report to a scientific meeting in Paris.

"We have found that large doses of Tanghinia extract will kill our animals, just like large doses of digitalis. In smaller doses Tanghinia slows and strengthens the heart, *just like digitalis.*"

They went home to Russia and began pestering their learned colleagues. "The French praised our report," they announced. "Now, where can we find some more of these ordeal poisons, more extracts that slow the heart?"

A big Russian explorer at Saint Petersburg spoke up. "Come over to my laboratory. I think I still have a little 'ipoh' there."

"Ipoh?"

"Yes. It's not an ordeal poison at all but an arrow poison. It comes from the Antiaris tree in Malaya. You have never read about the Antiaris tree? No? Well, it exhales a deadly perfume which kills any bird flying over it and any beast that comes near. You can always tell when you are approaching the Antiaris tree—for miles around it, there is nothing but the bones of dead animals. . . ."

The "deadly perfume" of the Antiaris tree might have been a legend, but there was nothing fantastic about the arrow poison. Good, sound laboratory tests proved to the Russians that it was murderous in large doses, but in small amounts it, too, acted like the Madagascar Tanghinia and like digitalis. Here were two possible substitutes for digitalis, two new chemicals to cure flabby hearts.

The ink on these Russian reports was hardly dry before scientists were writing letters all over Asia, Africa, and South America. They rushed requests to their friends and their government representatives. They begged assistance from leaders of tropical expeditions. "Please send us any arrow poisons or any ordeal poisons which the natives use."

At almost the same time, the first replies to these appeals reached England. The great Dr. Livingstone, way up the Zambezi River in southwestern Africa, described the effects of an arrow poison called *kombé*. It sounded so deadly that the scientists tingled in anticipation. Better yet, two packets of *kombé* arrived, one from another expedition in Africa and one from the British consul at Zanzibar.

The job of testing this chemical assassin was given to Thomas Fraser at Edinburgh. He was told only that the poison was made from the seed covering of the yellow-flowered Strophanthus vine, native to all Africa, and that the Russians had already been at work on *kombé* and turned out a preliminary report. All the rest was up to him.

Fraser turned out his first report in a hurry. "Like digitalis," he stated, "*Strophanthus kombé* has the property of slowing and strengthening the heart muscle of experimental animals." Then he learned how to handle his drug—now known as *strophanthus*—and to use it on sick human hearts. In 1885, exactly a hundred years after Withering had publicly announced the miracle of digitalis, Dr. Fraser went down to Cardiff and into the annual meeting of the British Medical Association.

"Gentlemen," he announced, "I wish to lay before you the results of treating dropsy with a new drug, strophanthus. It is a proposed substitute for digitalis, to which it seems to be related. Here are the results—with graphs—of four patients on whom I used it. . . ."

Fraser produced his evidence: he showed the condition in which his patients had come to him—swollen and waterlogged because of flabby, tremulous hearts; he showed how strophanthus worked—infinitely faster than digitalis; he showed how the hearts sud-

denly stopped their deadly puttering and began beating slowly, strongly, regularly; he showed how the stagnant fluid was picked up and flushed out of the drenched tissues.

When he stepped down from the platform, the good English physicians swarmed about him. They had only one question: "Dr. Fraser, where can we get this strophanthus?"

There was no doubt about it—strophanthus was good, just as good as Fraser claimed. Given in small doses, the arrow poison was a grand medicine for hearts. Except for the one disadvantage that, unlike digitalis, it must be given by injection and not by mouth, strophanthus might even have outshone digitalis itself.

Soon there were more of these digitalis-like remedies, exotic poisons from Malaya, India, Mexico, Brazil, the Philippines, and Africa. There were native remedies which had long been used against dropsy—Canadian hemp from America, autumn Adonis and lily of the valley from Russia, the familiar wallflower, and the Christmas rose, which Hippocrates had prescribed. There was ouabain, another horrible African arrow poison favored today by French heart specialists. At Johns Hopkins University, John Jacob Abel even checked on the esteemed Jamaica toad and found a digitalis-like compound in its saliva.

The crude knowledge of savage hunters and untrained peasants had yielded enough dropsy cures to last for many years. There was another heart disease, however, that neither digitalis nor strophanthus nor any other of these plant products could help. It was a disease marked by constant attacks of terrifying pain that started over the heart and then spread over the left shoulder, down the left arm. Doctors, hopelessly mystified, called it *angina pectoris*. . . .

V

It was early one morning in the winter of 1866. In a corner of a great ward in Edinburgh's royal infirmary, a flickering lamp fought bravely against the cold darkness. It shone on a bedside, a nurse,

two doctors. They stood there motionless, watching their patient.

Finally one of the doctors turned away, shivering. "It's cursed cold," he muttered. "What hour d'ye make it?"

The other doctor, the younger one, looked at his big gold timepiece. "It's coming on to two o'clock, sir. Most any minute now, and he'll have it."

They turned back to the patient. He was wet with perspiration, miserably frightened, appealing to the doctors with his eyes.

Young Dr. Brunton, scarcely twenty-three years old, spoke up again, very softly. "Every night for the last three weeks he's had the attack. Comes between two and four in the morning. It lasts for a full hour or more."

"I know that," old Dr. Bennett scowled. "I've seen angina pectoris before, but never have I seen one like this!"

Brunton looked back to the bed, but nothing had happened yet. "That's why I suggested this new experiment," he continued. "We've tried everything else—digitalis, aconite, lobelia, brandy, chloroform—but none of them does any good."

"I suppose we might as well try this new thing o' yours," Bennett agreed. "But what makes you so sure it'll work?"

"I'm not sure, sir, not positively. But I do think that angina pectoris has something to do with high blood pressure—that is, with sudden attacks of high blood pressure. That'd be the only thing that might explain why Mr. McCollum, here, felt better when we drew a little blood yesterday in the middle of his attack. As far as I can make out, the only thing that bloodletting did was to reduce the pressure in the blood vessels."

"Aye," Bennett said. "And you think your chemical will do the same as the bloodletting? You think it can diminish the blood pressure, eh?"

Young Brunton fidgeted. "I don't know, sir. That I don't. I've never tried it on a patient. But on a dog, sir, it works beautifully!"

"O' coorse," Bennett muttered to himself, "on a dog it works beautifully, does it now? On a dog. Hm-mm, phoosh!"

Suddenly the nurse interrupted. "I think Mr. McCollum will be needing you now, doctor. The attack is starting."

Mr. McCollum was obviously facing some imminent terror. His face, once ruddy and moist with sweat, had now become drawn and white. He seemed paralyzed with fear. "O God," he whispered hoarsely, "it's a-comin' now. It's a-comin'! This time it'll kill me sure. I know it, it'll kill me! I canna stond it!"

Dr. Bennett walked over quickly and gripped the patient's shoulder. "Easy now, McCollum. Easy does it, mon. We'll fix ye up shortly." He turned to young Brunton. "The pain's comin' now. See, watch it! Ah, now it's here!"

McCollum gasped in agony as the terrible pain clutched his heart. In vain he tried to frame a cry for help.

Bennett stood up and mopped his forehead. "Well, Brunton?" he called.

"Well, sir?"

"Dr. Brunton, Mr. McCollum is—all right, he's now your patient. Go ahead and do what ye like. And I'd suggest ye do it r-r-rapidly, doctor!"

Brunton gulped. "Thank you, sir," he said. Out of his pocket he pulled a tiny vial filled with a pale-yellow fluid. "Nurse, pass me that cloth."

On a bit of gauze, Brunton counted out ten drops of the fluid, smelled it quickly, and then pushed it under McCollum's nose. "Inhale, now, Mr. McCollum. Inhale, a good deep breath, if you please!"

The straining McCollum couldn't help but inhale those sweet vapors. One breath—another—and another.

And the doctors—they stopped breathing entirely as they saw McCollum's face turn from white to red, his tense muscles relax, the pain wash from his body.

McCollum finally pushed the gauze from his face and smiled weakly. "Bless ye, doctor," he whispered, "the pain is a' gone. Ye've stopped it!"

Old Dr. Bennett whispered, too, as he put away his watch. "Stopped it, he did . . . and in theerty seconds! I'll be eternally domned!" He flicked his tongue over parched lips. "Brunton, me lad, what d'ye call that stuff ye used?"

"This," answered Brunton, "is nitrite of amyl. It worked the same way on the dogs."

And so Dr. Lauder Brunton, the immortal "Tommy" Brunton of Edinburgh, discovered a drug for angina pectoris. It was a monumental discovery, for it came from no folklore or tribal custom. It came right out of the laboratory.

It worked, although Brunton had only half guessed the reason. It was true that the pain of angina pectoris did have something to do with high blood pressure, but it was a very strange kind of pressure. It was a spasm, a sudden constriction of the vital arteries which nourish the heart muscle itself.

Amyl nitrite possesses the miraculous power of relaxing those arteries, of letting the blood flow through again. It can't cure angina pectoris. It can, however, reduce the pain or even prevent it completely.

Young Brunton announced his discovery in a report which was published the following year, in 1867. Unlike Withering, he needed no book to describe his findings. Two short columns in a medical journal were enough to tell the story. They were enough to make Brunton one of the heroes of medicine, a man who could kill pain with a few drops of liquid poured out on a piece of gauze.

Ten years later in London, another epoch-making discovery brought further relief for angina pectoris victims. Doctors were astounded at the identity of this second remedy, for it was not new at all. It had been known and feared for a good many years. It was *nitroglycerine.*

In his London office, Dr. William Murrell was investigating nitroglycerine for the most uninspired reason—to settle an argument. There was no argument about its explosive powers, but there was a

bitter dispute between two schools of physicians who did not agree on what it could do, taken internally, to the body.

Dr. Murrell chose a bad time to perform his test. Waiting for a patient one afternoon, he pulled a bottle of tincture of nitroglycerine out of his pocket, removed the cork, and touched the wet end to his tongue. He swallowed a drop or two and then, as his patient arrived, promptly forgot about it.

Before the patient had listed even half his troubles, Dr. Murrell realized that he himself was by far the sicker man. It was as much as he could do to stall for time, to ask his patient to go behind a screen and undress for an examination.

"I regretted that I had not taken a more opportune moment of trying my experiments," he wrote later. "I was afraid the patient would notice my distress and think I was either ill or intoxicated."

Poor Murrell wouldn't have bet a shilling on his life at that point. His pulse was racing, he couldn't breathe, his whole body felt bloated, and his head resembled a balloon. Every heartbeat shook his body. He had every expectation of finding himself the center of a very large explosion.

Somehow or other, he managed to get through with his patient. Then he dropped woefully into his chair. He had never felt worse in his whole life, but he was sure of one thing—he had undoubtedly taken an overdose of nitroglycerine, and the symptoms he felt were identical with those produced by an overdose of amyl nitrite!

He vowed to try the stuff—if he lived—in smaller doses. He must try it on other volunteer experimenters. He must try it on patients!

The patients liked it. Those who suffered from angina pectoris found that nitroglycerine relieved their pains just like amyl nitrite. Explosive nitroglycerine, pride of the army, became blessed nitroglycerine, pride of the heart specialists.

It had taken more than a hundred years to find them, but the heart doctors finally could boast of three different families of drugs: first and foremost, digitalis; second, the arrow poisons, headed by strophanthus; and third, amyl nitrite and nitroglycerine for angina pectoris. All of them were in actual use by 1900.

Today, there are hundreds of men engrossed in a search for other and better heart drugs. It is imperative that their search succeed; partial conquests over dropsy and angina pectoris have solved only a pitifully small part of the problem. Today the still incurable diseases of the heart and the blood vessels—high blood pressure, hardening of the arteries, and a dozen more—lead all other causes of death. They are the Number One Killers of modern civilization.

The hunt must go on!

CHAPTER IV

Blessing from Hell

KOLLER AND COCAINE

"STEP OVER here," said Don Pablo. "This is what you should see."

Shivering from the intense cold, gasping for breath in the thin mountain air, Augostín de Zárate moved closer to the mouth of the mine. An old Indian foreman bowed silently to the two Spaniards.

"Are the men coming out?" Don Pablo asked.

"I call them, master. They come soon."

De Zárate wrapped his coat tighter about his trembling shoulders and tried to control the chattering of his teeth. "By the saints," he sputtered, "they told me down in Lima that you had to be a mountain goat to get gold out of Peru, but they didn't tell me that one's blood would freeze to ice!"

Don Pablo laughed harshly. "For gold and silver, señor, we do many things we do not enjoy. The Incas could work this mine. So can we!"

The men turned as the first crew of miners filed out—tall, dark Indians covered with dust and dirt. De Zárate gasped. "Look! They are naked—just a tiny belt around the waist. But surely they will freeze!"

"No," replied Don Pablo, "they're perfectly comfortable. Hola, foreman, come here! Tell this gentleman when the slaves took their food."

The old Indian was puzzled. "Their food? Master, you know. You give the orders. They eat last when they go into mine. Yesterday at the rising of the sun."

Don Pablo turned to De Zárate. "There, you see?"

"What? Good God, señor, they went to work yesterday morning! *Thirty-six hours ago?* That is impossible!"

"Not at all, my dear De Zárate. These natives are used to work. They are not your soft Spanish peasants."

"Incredible, Don Pablo, utterly incredible! They work thirty-six hours without sleep . . . and without food?"

"They have touched no food since they entered the mine."

"And water?"

"Same thing. They get along without it."

"I still cannot believe it, Don Pablo. I swear to you on my soul, this is the most amazing thing I have ever . . . but how do they do it?"

Don Pablo pointed to the Indians crouched on their heels, each bending over a pair of pouches. "Watch them, señor."

Peering over their grimy shoulders, De Zárate saw each native pull a handful of dry, crumbly leaves from one pouch, dip them into gray-white powdered lime from the other, and roll them into a wad which was deftly popped into his mouth. He saw the Indians start chewing blissfully, relaxing with satisfied grins.

"What is that?"

"That," said Don Pablo, "is the secret. It came to us from the Incas along with their gold. That lets these men go without food and water. That keeps them warm while we freeze. That makes brave men out of cowards. That makes possible the long hours of work without fatigue, and the shiploads of yellow gold for the King of Spain. That, Señor de Zárate, is the coca leaf!"

"Coca," De Zárate repeated, "the magic plant of the Incas? But surely, I thought . . . it was merely a legend."

Don Pablo swore. "Ah, a legend! Yes, that is what the priests would have you believe. They say the coca leaf is worthless, no good at all. They tell you the whole thing is a superstition. They preach that this notion of the natives is just an illusion of the devil. Well, now, you have seen it. What do you think?"

"What do I think? I think it is fantastic! If I can accept your word that it does all the things you say . . ."

"You can stay here as long as you like," Don Pablo interrupted, "and see for yourself."

"No," De Zárate conceded, "I believe you. I believe every word. And yet, when I tell all this in Spain, the question is—will they believe me?"

And so in 1555 the Spanish explorer Augostín de Zárate fearfully made his report: "In certain valleys, among the mountains, there grows a certain herb called Coca, which the Indians do esteem more than gold or silver. . . . The virtue of this herb found by experience is that any man having these leaves in his mouth hath never hunger or thirst. . . ."

It was the introduction to the fabulous story of Peruvian coca.

It began like an unbelievable, fantastic fairy tale, only to unleash a horror over all the civilized world. It involved hundreds of men in one of the worst scandals in medical history, and it made possible the most surprising triumph in man's battle against pain.

II

While the magic plant of the Incas was being groomed for its introduction to the world, another powerful compound was discovered in faraway Leipzig, where a German pharmacist taught the mysteries of his profession to his nephew, Valerius Cordus.

Cordus was an impatient young apprentice. He disliked ordinary pharmacy with its sloppy descriptions, careless compounding, and superabundance of names and names and names. (It was this feeling which led him to prepare the world's first pharmacopoeia, a legally sanctioned list of standard drugs with standard directions to prepare them.) He also disliked experiments, at least the incredible, hopeless experiments of his colleagues who cooped themselves in musty back rooms while seeking to make gold out of lead or find perpetual youth in a concoction of salamander's gills, wasp's eyes, ancient eggs, and filthy excrement.

Cordus preferred simpler research. "Good Uncle," he called one day, "look at what I've found!"

Uncle looked with mixed fear and boredom. Sometimes his nephew's experiments failed to work at all, and sometimes they exploded.

"Now," lectured the young man, "I take strong oil of vitriol and put it in here, so. Then I add a little distilled spirits, carefully, just . . . like . . . this. And then I stir. See how nicely it boils and fumes. And now, Uncle, come closer and smell this vapor."

The old man leaned over, sniffed suspiciously, and then pulled back. "Phew! Horrible smell!"

"Horrible? No, Uncle, it's nice and sweet. It won't hurt you—go on, take a real deep breath."

Shaking his head in despair, Uncle offered himself once more. He inhaled the fumes deeply, again and again. Then he stood back ready to add further caustic remarks to his original description, but the remarks were never made. The whole room tilted grotesquely on end and began to spin, slowly at first, then in a dizzy spiral that sent chairs, tables, shelves, windows, and door flying like rockets. In a moment his head cleared, and the room slowed to a stop. He was sitting on the floor, and above him young Cordus stood watching, grinning like an impudent elf.

"Isn't that odd, Uncle?" he asked pleasantly. "The same thing happened to me yesterday."

"Out of my house!" howled Uncle. "Get out, you brainless idiot! Why did I ever let you come here in the first place? Out, I say, out!"

Still grinning, Cordus retired to his own room and jotted down in his notebook that he had mixed oil of vitriol with distilled spirits and producer a vapor which could best be described as "sweet oil of vitriol." It made one very dizzy, he appended, and once a few inhalations seemed to stop the pain of "racking cough." And with that he forgot all about it.

Centuries later, chemists would read over his notes, translate the words "oil of vitriol" to sulphuric acid, "distilled spirits" to alcohol, and "sweet oil of vitriol" to *ether.*

Cordus, however, had so many experiments to perform that he paid no further attention to this strange, new gas. Anesthetic ether

joined Peruvian coca on the shelf and settled down for three hundred years of undisturbed uselessness.

Two hundred and fifty years later, in 1799, while Sertuerner hadn't even started to hunt for morphine and while patients still screamed under the flashing knives of surgeons, a third new compound was discovered. In London, a twenty-two-year-old chemist published a long, rambling manuscript entitled *Researches, Chemical and Philosophical, Chiefly Concerning Nitrous Oxide, or Dephlogisticated Nitrous Air, and Its Respiration.* The author was brilliant Humphry Davy, one of the greatest chemists of his times.

Davy sniffed at his new gas and was amazed as his senses whirled and wonderful dreams floated into his brain. He, too, hovered on the brink of a great discovery—"In one instance, when I had a headache from indigestion, it was immediately removed by the effects of a large dose of gas"—but he failed to take the final step. Nevertheless, he did try it on small animals, unfortunately in such large doses that they died, and more carefully on all his friends. He gingerly suggested that "it might have interest to the Surgeons."

But Davy was too busy making other experiments on other gases, and the surgeons were too busy trying to "cut for the stone in less than three minutes" to see the thing through.

Coca and ether were joined on the shelf by nitrous oxide, *alias* dephlogisticated nitrous air, *alias* laughing gas.

Thirty years rolled by, and the three forgotten anesthetics were joined by another. In 1832 the discovery of chloroform was announced simultaneously from three different countries. Justus von Liebig, father of modern German chemistry, reported it from his laboratory in Giessen; Soubeiran synthesized it in France; and the American Dr. Samuel Guthrie announced his finding from Jewettsville, New York.

Strange as it seems, chloroform was forgotten along with coca, ether, and nitrous oxide. Chloroform was an interesting compound, chemically speaking, but who cared?

Today it seems utterly incredible that four powerful painkilling anesthetics could have been known for years—two of them for

nearly three centuries—before medicine took notice. But it was not until 1842 that their miraculous powers were rediscovered and doctors kicked their heels in the air and cried, "By Heavens, here is what we've been looking for!"

In a space of five short years, the whole amazing revolution took place. Who started it? Who deserves the credit for that magnificent triumph? Today, a full century later, any attempt to answer that question seems completely hopeless. It has baffled the Royal Society of Medicine, the French Academy of Sciences, and the Congress of the United States.

All that seems certain is this: in 1842 there were no anesthetics. "You made your man drunk, and the porters and students held him down, and you had to set your teeth and finish the job fast!"

In 1847, thanks somehow or other to surgeon Crawford Long of Athens, Georgia; dentists William Morton and Horace Wells of Boston; chemist-physician Charles Jackson of Plymouth, Massachusetts; and the great Edinburgh obstetrician, Sir James Simpson, there were three blessed anesthetics—ether, chloroform, and nitrous oxide.

It happened so fast that the medical world was for once virtually speechless. The banishment of pain had revolutionized surgery.

III

But there was still Peruvian coca.

Discovered by Europeans early in the sixteenth century, it remained practically unknown, a botanical and pseudomedical curiosity, for two hundred years until the young South American countries rose in impertinent fury and removed the last vestiges of Spanish control. Then other Europeans came to study—French geographers, English naturalists, German botanists, Italian zoologists, even a sprinkling of Americans; and these new explorers rediscovered the coca tree.

That rediscovery brought a lot of questions. "What is the coca

tree?" these new scientists were asked. "Is it the same as the *cacao* tree of Brazil, the tree that supplies cocoa and chocolate?"

The scientists looked very wise, pulled out their textbooks, compared leaves, flowers, and bark, nibbled the seeds, wrinkled their noses, and answered: "No, the two trees are not the same. Brazilian cocoa or chocolate comes from the cacao tree, which should be classified as *Theobroma cacao.* We find, upon consulting the taxonomy key and classification systems of De Candolle, that the Peruvian coca tree is more properly called *Erythroxylon coca.* It would be possible to go into this matter in greater detail, but, in a word, the trees are different!" That settled that.

But there were other and more important questions. "What about this coca tree and all its beautiful legends? Is there any truth to them? Can coca leaves really perform the miracles the Spaniards reported?"

Any truth! Why, the Spanish stories hadn't told the half of it! The new explorers fell all over themselves telling how really remarkable, how astounding, how miraculous these coca leaves were. Coca wipes out the need for food, for water, for sleep! It overcomes cold and heat! It cures any sickness and banishes any sorrow! It makes giants out of cowardly weaklings! Is coca *good?* . . .

But in spite of all this rhapsodizing, there were still two schools of thought on coca. The second school was definitely in the minority; it consisted of two lone Germans who admitted that coca might be able to induce some mighty splendid reactions, but they also claimed other and less heroic effects.

"We have seen coca-chewers," they said, "and we have noted something else—their bad breath, their pale lips, their greenish, stumpy teeth, their unsteady gait. We've seen their yellowed skin and dim, sunken eyes. We've seen what happens to white men who start chewing coca—we've seen that they start and *can't stop!*"

The majority party was both shocked and pained. "Can't stop? Oh, rubbish!" they scoffed. "You're getting it confused with opium. Those splendid, health-giving coca leaves? Impossible!"

And then these scientists, these men who were so thrilled with coca's wonder, dismissed the opposition with one simple blow. "This so-called 'addiction' reported by our esteemed German colleagues," they concluded, "could have a very simple explanation. Either Herr Poeppig and Herr von Tschudi are placing too much weight on a few rumors they have heard, or—if they actually did see these things themselves (which we wouldn't dare doubt)—they are assuming that a few exceptions are generalities. But as for us, we have never seen such things. And, after all, one has only to look at the wonderful things that coca can do . . ."

That old routine—"Coca prevents hunger. Coca prevents thirst. Coca overcomes exhaustion. Coca brings exhilaration." Repeated over and over, those phrases grew remarkably convincing.

In Paris, young Dr. Angelo Mariani caught himself humming the Utopian chant. "If coca can do all that in Peru," he mused, "why can't it do the same things in France? We could use a medicine like that, a tonic to overcome hunger, exhaustion, and cold. Perhaps that lovely coca tree would grow here in Paris, possibly even in my own garden."

The coca trees would not thrive in Paris, but the leaves could be easily imported from South America, and within a few years chemist Mariani was importing pounds and pounds of them, putting them up as "Mariani wine," "Mariani elixir," "Mariani lozenges," "Mariani tea," and "Mariani pastilles." The young chemist rubbed his hands in glee as orders poured in from every corner of the civilized world. More and more doctors tried it, liked it, and prescribed it.

Dr. Charles Fauvel of Paris used the new products to treat hoarseness and sore throats, and he sent in a helpful testimonial: "Thanks to Mariani wine, I have been able to restore the voice of many lyric artists who would have been unable without this potent agent to give their performances."

Said Marius Odin (Doctor of Medicine, Professor, Chevalier of the Legion of Honor, etc., etc.): "This young woman complained of weakness and general atony, headache, dizziness, vertigo, tendency

to lipotynie caused by sorrows, sitting up late at night, and general depressing influences. . . . There was insomnia and a tendency to night sweat. I prescribed Mariani wine. At the end of a month's treatment, her state was most satisfactory."

A stalwart French priest, Abbé Pullez, reported: "I should like to call your attention to the marvelous effect of coca in weakness of the voice; every time I have to preach a long sermon, I take coca for two days before and obtain thus a sonorous and increased volume."

More glowing testimonials arrived—from the physician in chief of the French army; from Boston ("it dissipates 'the blues,' leaving the mind calm"); from London ("a valuable stimulant"); from New York ("an excellent general tonic"); from Columbus, Ohio ("a tonic in dyspepsia and nervous prostration").

Coca, it appeared, could cure anything—stomache-ache, indigestion, headache, dizziness, weakness, pallor, sore throat, anemia, nervous exhaustion, diabetes, Bright's disease, gout, rheumatism, irritability, insomnia, heart disease, constipation, tuberculosis, malaria, goiter, convulsions, seasickness, syphilis, and at least four kinds of pip.

Most doctors considered Mariani's advertising accurate, particularly since he also gave the strict warning: "Beware of substitutes." But there were other dangers more horrible than substitutes, dangers of which no word was said.

There was a good reason why the assorted Mariani coca products were declared to be so effective. In 1860, Albert Niemann reported in Germany that he had examined coca leaves and successfully isolated the long-sought active principle.

"It is a pure chemical, an alkaloid," he announced. "To it I have given the name—*cocaine.*"

IV

Niemann's announcement of the discovery of cocaine was coupled with another and even more significant report. "In placing

some of the cocaine in my mouth," he described, "I noted to my surprise that my tongue became numb. I could not taste nor distinguish between hot and cold. . . ."

To his surprise! Here was a chemical, a pure drug that would wipe out sensation, that would eradicate any kind of feeling, that produced a local anesthesia!

Unfortunately Niemann was a chemist, a good chemist, but not a physician. If physicians would have sold their souls for a drug like that, he never dreamed of it.

Neither did a Viennese pharmacist, three years later, who noted in an inconspicuous journal that cocaine produced numbness in the tongue, the mouth, and the throat.

Neither did a German eye specialist, who laughingly described this cocaine numbness before a group of ear-eye-nose-and-throat doctors.

A Russian physiologist wrote a long, scientific paper on the interesting insensitivity produced in his animals by applications or injections of cocaine solutions, and a Peruvian physician used cocaine compresses to cure painful bruises and actually wiped out the pain; but both neglected to make a real point of it.

One man, Thomas Moreno y Maiz, former chief surgeon of the Peruvian army, made a serious study of cocaine. "They say that coca prevents hunger, that it reduces the need for food," he said to himself, "but does it?"

He took good fat rats, put half of them in one cage, and let them starve. The other half he put on a diet of coca. Day by day he watched the animals as they slew a perfectly good legend. The rats fed on cocaine died of starvation even faster than the poor rats who were fed nothing.

He took slippery bullfrogs, cursed them while he tried to knot threads around their wriggling legs, and finally tied them down to his table. He injected a solution of cocaine into their hind legs, and he poked those injected legs with sharp needles—the animals should have jumped, but nothing happened.

"The sensitivity in the injected limb," he wrote down, "completely disappeared."

He next jabbed his needles deep into the legs until they hit the motor nerves. Ah! Now the animal moved!

"The *sensation* is completely abolished," he noted, "but strangely enough, *motility* still persists."

Then he tried his needles on the front legs, the ones that had not been injected with cocaine. These were exquisitely sensitive, and each jab made the frog jerk with pain.

Moreno y Maiz concluded: "The local action of this substance is very marked." Then as a note, an afterthought, he added, "Could one utilize cocaine as a local anesthetic? One cannot make a decision on the basis of such a limited number of experiments; it must be decided by the future." Thus the good Peruvian scientist threw fame right out of the window.

Other scientists and physicians readily confirmed his laboratory findings, but they, too, were unwilling or unable to carry them further. If Opportunity is a lady, at that point she undoubtedly stamped the floor, tore her hair, and screamed.

V

One hot morning in the summer of 1884, three young doctors sat glumly in an office of the great General Hospital in Vienna. Two of them scowled alternately at each other and then at the ceiling, while the third read through the pages of a patient's report. Finally he finished, placed the report on his desk, and turned to his visitors.

"Frankly, gentlemen," he said, "there seems to be only one possible conclusion. You've got a patient here who—well, Dr. Freud, I hesitate to put it so bluntly, but he seems to have become addicted to cocaine."

Sigmund Freud winced. "Pardon me, Dr. Breuer," he exclaimed, "but I can hardly believe that. My patient may be poisoned by

cocaine. I may have given him too much. But addicted? That I cannot possibly understand. Cocaine is not addicting. The method I used, the American method, has been found thoroughly reliable."

"Just what is this 'American method' you used?" asked Breuer.

"Well, it's a procedure that was worked out ten years ago by a Dr. Bentley in Kentucky. This American discovered that morphine addicts and alcohol addicts can be cured by administration of cocaine. It's really a wonderful treatment, Dr. Breuer!"

"Wonderful?"

"Indeed," Freud assured him. "I am confident that in a few years, by using cocaine, we can completely wipe out morphine addiction."

Breuer shrugged eloquently as he picked up the report again. "I hope you're right," he said, "but this case here doesn't exactly speak highly for your American method. Now, as I understand it, this patient is a physician who became addicted to morphine after undergoing an amputation of the left thumb. Correct?"

"Exactly. We tried to stop the morphine, but he suffered so much after the withdrawal that we gave him cocaine instead."

"And that stopped the craving for morphine?"

"Absolutely," said Freud.

"But when you tried to stop administering cocaine?"

Freud wriggled uncomfortably in his chair, "Well, that's what I can't understand. As soon as I ordered the cocaine stopped, the patient began complaining of hallucinations, delusions. . . ."

"He saw snakes, it says in the report."

"Yes, snakes and dragons and indescribable horrors, Dr. Breuer. He thought these beasts were trying to catch him." Freud leaned forward on the edge of his chair. "But I'm sure this is an unusual case. I don't think it's at all typical."

Breuer said, "That may be true, but what do you intend to do about it?"

"Experiment, sir. We want to perform a lot of tests with cocaine —tests on human beings. We'd like your permission to use the laboratories and the necessary apparatus."

"I suppose that will be satisfactory. Who'll do these tests?"

For the first time during the meeting, the third man spoke. He was twenty-year-old Carl Koller. "Dr. Freud has asked me to work with him on this project," he said. "I'd planned to invite my friend, Dr. Koenigstein, to join with us."

Breuer looked at the short, quiet youth. "Good," he said, "I've heard of your work, Koller. Let me know how things go."

So three men started to investigate the effect of cocaine on human beings—Sigmund Freud, who would one day win worldwide attention for his work on psychoanalysis, Carl Koller, and Leonard Koenigstein. Laboring for weeks on the remarkable chemical, they tried it first on guinea pigs and rabbits and finally on themselves. They tested its action on blood pressure, on pulse rate, on respiration. They filled page after page with scrawled notes and graphs.

After a long series of these tests, Freud announced he was going off on a vacation. "I've worked out my clinic schedule so I can get away all right," he said. "I think I'll go to Holland and—well, there's a young lady there I want to see. You boys will get along nicely without me. Better try taking the stuff by mouth and see what it does to respiration. Try yourselves on the dynameter, too. And you might see what it does on sores." He was off.

Koenigstein glanced at Koller. "Well," he exclaimed, "it seems our good friend doesn't want *us* to have a vacation. But that last idea of his . . . you know, I wonder what cocaine might do in eye infections. I'm going over to the clinic tomorrow and try it on trachoma."

"Um-hmm," Koller agreed. "Might be something to that."

More weeks passed, and the two stay-at-homes kept hard at work. Koenigstein fretted at cocaine because it would not cure eye infections. Koller stayed with his respiration tests.

This Koller was actually a splendid laboratory worker, already credited with a brilliant piece of research on embryology and with months of good training in testing the effects of poisons on living animals. But this cocaine business—it was slow and difficult, and

it was beginning to bore him. Koller, who intended to become an eye specialist, resented giving up so much time to cocaine when he might have been listening to the great Viennese ophthalmologists.

One of those lecturers had upset Carl Koller. "Gentlemen," the professor had said, "ophthalmology today has the greatest need for a new drug—for a local anesthetic. We cannot perform operations on the eye with general anesthetics, with ether or chloroform or nitrous oxide. They are too dangerous for eye surgery; they are followed too often by nausea and vomiting, which destroy the delicate repairs on the eye. And unfortunately, too, we cannot use morphine or chloral or bromides. Until we find a compound that produces local anesthesia when dropped into the eye, we are helpless to treat cataract, iritis, and a vast number of eye diseases. . . ."

Cure blindness!—that's what such a drug would do. It would cure blindness by making it possible to operate on the eye. If there only were such a drug. . . .

That thought continued to plague Koller as he climbed up to the laboratory, as he prepared a fresh solution of cocaine, as he idly flicked a few drops on his tongue.

Oh, if there were only a drug that could produce local anesthesia just as this cocaine was making his tongue feel numb. Just as—what!

He put down the bottle and very, very slowly touched the tip of his tongue to his teeth. No feeling. He stuck out his tongue and first tapped and then pinched it with his fingers. No feeling, no pain. Of course, cocaine produced local insensitivity—everyone knew that, but no one had ever done anything with it.

"Leonard!" he called. "Leonard Koenigstein!"

"Hello!" the answer came from the next room. "What's happened?"

"Leonard, I've got it! I've got a local anesthetic for the eye! It's cocaine!"

"What? You're crazy! Have you tried it yet?"

"No," whispered Koller, half to himself, "I haven't tried it yet, but I'm going to. Right now!"

Quivering with excitement, he picked up his flasks and his instruments, rammed them into his pockets, and almost flew out of the room. "Animals!" he muttered. "Animals! Who's got some animals? I know—Stricker's laboratory!" He turned and headed for the experimental pathology department.

Dr. Stricker's laboratory was empty. Koller glanced around impatiently. "Boy!" he shouted. "Where are you?"

"Here I am, sir." A young assistant stepped out of a storeroom. "Can I get anything for you?"

"Yes. I want some frogs and a couple of guinea pigs. I want you to help me for a minute, please."

While the assistant held the first squirming green frog, Koller filled a syringe with his cocaine solution and carefully squirted a drop into one of its eyes. "Hold him carefully, now," he breathed. "I don't want any of that solution to run over to the other eye."

They waited for thirty seconds, a minute, two minutes. Then Koller picked up a probe and carefully moved it towards the frog's *untreated* eye. At the first touch, the animal struggled to pull away. "Ah, that hurts him! Splendid! Now let's try the other eye. Careful there, damn him—hold him tighter!"

Again Koller tried, this time on the eye that had been doused with cocaine solution. And this time—miracle of miracles!—the frog didn't even budge. Koller touched the delicate surface of its eye with the probe. Nothing happened. He pushed a little harder, and still nothing happened. He scratched the eye, gently at first and then good and hard. Any ordinary frog would have leaped out of reach in a moment, but this one seemed merely bored.

"I'm right!" Koller announced. "The cocaine has absolutely anesthetized that eye. It no longer feels pain. Cocaine is the perfect local anesthetic!" He turned to his unimpressed assistant. "Don't you agree with me?"

"Certainly, sir. I always agree with the doctors."

Koller chuckled. "Go get me a guinea pig, and we'll try it again."

The guinea pigs were bigger animals and easier to handle. They were treated with the cocaine solution, and the first results were

brilliantly confirmed. Koller pulled out a book and scribbled his notes:

"For first minute, slight irritation; animal blinks, contracts eyelids.

"Anesthesia starts immediately after, lasts approximately ten minutes with three drops of 2 per cent cocaine solution.

"During anesthesia animal shows no sign of pain from following tests: needle scratch on eye, puncture of eye, cautery with silver nitrate, deep incision."

Animal after animal was tested, each showing the same reactions. There couldn't be any question about it—cocaine produced a complete loss of sensation, localized to its site of application. But how about human eyes? Koller let the solution be dropped into his own and stood quietly while Koenigstein and the other doctors touched the usually sensitive cornea with the head of a pin. It was unbelievable, and yet the proof was there before them.

"What are you going to do with this thing?" they asked.

"First," said Koller, "I'm going over to the eye clinic. There's an operation scheduled today for removal of a cataract. They plan to do it without an anesthetic and let the poor devil scream. I'm going to give them a surprise!"

A surprise? The doctors in the operating room were dumfounded; they had come expecting to steel themselves against the patient's cries and groans, but here he sat wide awake, smiling, and perfectly comfortable while the surgeons cut the blinding film from his eyes.

Koller's next stop was the laryngology department, where Dr. Jellinek finally agreed to let cocaine be used to spray the throats of his patients before surgery. In a few hours, the story of the amazing new anesthetic had spread through the hospital. The dignified, bearded surgeons all bowed to Dr. Koller. The interns slapped him enthusiastically on the back. The patients whispered as he passed by.

Sigmund Freud returned from Holland just in time to discover that Koller had become famous.

It was necessary that the discovery be announced at once. Was there a meeting, a convention, where Dr. Koller could present a formal report? Fortunately there was—the German Ophthalmological Society was to meet at Heidelberg shortly. It was a splendid opportunity, for the ophthalmologists were just the men to hear how cocaine could be used on the eye. Could Dr. Koller attend that meeting?

Unfortunately Dr. Koller could not. There would be railroad fare, hotels, meals, and Heaven knew how many other expenses, and the tragic truth was that the young hero had no money. Instead, he asked his good friend Dr. Brettauer, who planned to attend the meeting anyhow, to present a report for him. Practically heartbroken, Koller remained in Vienna.

On September 15, 1884, just a few weeks after Koller had first made his discovery, a group of doctors gathered in a small room in Heidelberg in answer to a special invitation. This was not the regular meeting of the Ophthalmological Society but a special preview. The official announcement, if all went well, would be made the next day.

This first audience had been carefully selected. It included Professor Arlt of Vienna, Professor Becker and several other men of the Heidelberg staff, Dr. Noyes of New York, and Dr. Ferrer of San Francisco.

Before this select assemblage, Dr. Brettauer rose to speak. "Gentlemen, I have been asked to present to you a paper which was prepared by a friend of mine in Vienna. He is Dr. Carl Koller, who is intern and house surgeon at the General Hospital. His experiments are so startling we thought it would be better to describe them first to a small group. Now, if you will permit me, I shall first read Dr. Koller's manuscript. He says, 'It is a well-known fact that the alkaloid cocaine . . . makes the mucous membrane of the throat and mouth insensitive. . . . This led me to investigate the

action of this agent on the eye. I have reached the following conclusions . . .' "

As Dr. Brettauer read Koller's carefully prepared notes of the experiments on frogs and guinea pigs, the listening doctors nodded knowingly. But when they heard the climactic description of the effects of cocaine on human eyes, of an eye operation with cocaine, their own eyes bulged, and their mouths sagged in sheer astonishment.

At the end of the reading, Dr. Brettauer put down the manuscript. "I know your reactions to this report, gentlemen, must be very much like mine when I first heard it. Undoubtedly it sounds impossible. We have therefore arranged to show you what cocaine can do. Dr. Becker has kindly placed one of his patients at my disposal. And now, Dr. Becker, if you please!"

Dr. Becker signaled to an orderly who stepped out of the room and returned in a moment with the frightened patient. He was placed in a chair, and Dr. Brettauer walked over to him.

"Please relax," he said. "I'm just going to put a few drops of this liquid in one eye. It won't hurt. Open now . . . ah, one, two . . . that's it! Now blink and lean back." He turned to his colleagues. "Please step closer, gentlemen, and tell me if you detect any sign of pain."

He picked up a probe and pressed it against the patient's anesthetized eye. He rubbed the surface of the cornea. With a speculum he spread apart the eyelids until it seemed they were ready to tear. With a forceps he grasped the eyeball and pulled it back and forth.

He stepped back and looked at the patient. "Tell me, did that hurt?"

"I felt nothing, doctor."

Delicately, now, Brettauer touched the eye which had not been treated with cocaine. The patient snapped back his head in pain.

Dr. Brettauer turned once more to his audience. "I think you will agree now that Dr. Koller's report is entirely accurate!"

A man in the back of the room sighed as though he had been holding his breath all during the demonstration. "Astounding!" he breathed. "Now I can cure blindness!"

A month later, Koller discovered for himself how it felt to make a historic announcement. Before the meeting of the Vienna Medical Society, he thrilled to the applause that greeted his own reading of the report.

There was, however, one upsetting incident that marred the evening. Another doctor went to the platform and described how he had discovered the anesthetizing properties of cocaine. It was Leonard Koenigstein, the man who had worked with Freud and Koller, the man who had tried in vain to cure eye infections with the drug. He gave no credit to Koller.

A few hours later, when it appeared that a nasty fight for priority threatened, Sigmund Freud saved the day. With another doctor he walked up to Koenigstein. "Dr. Koenigstein," he said quietly, "you know Dr. Wagner-Jauregg, don't you?"

"Of course," answered Koenigstein. "How are you tonight, doctor?"

"Very well, thank you." Wagner-Jauregg's voice was alarmingly cold and brusque. "Koenigstein, let's come to the point. Freud and I both heard your remarks this evening. I think you will agree with us that any dispute over the discovery of cocaine would be extremely unfortunate. There would be entirely too much notoriety and scandalmongering. Do you follow me?"

Koenigstein began to perspire. "No, gentlemen, I haven't any idea . . ."

"Perhaps I can help you," interrupted Freud. "We are a little distressed that in your paper tonight you seemed to give the impression Koller had nothing to do with the discovery of cocaine as a local anesthetic. Just exactly what are your ideas on that subject?"

For a moment Koenigstein stared at the two men. "I—I think I understand you now, gentlemen. What do you suggest?"

Freud nodded. "Splendid. We appreciate your co-operation. I think a letter to the editor of one of the medical journals with full details on Koller's part in the discovery would be completely satisfactory."

"Very well, doctor." Koenigstein bowed stiffly. "I shall write the letter tonight."

Sigmund Freud and Julius Wagner-Jauregg, a future Nobel prize winner, had saved the cocaine discovery for Koller.

One disappointment had been averted, but there was another in store for the man of the hour. Koller had hoped to be appointed assistant in one of the two great Vienna eye clinics and had counted heavily on his cocaine work to ensure the appointment. But, as in any big hospital, there were wheels within wheels, political machinations, religious prejudices. "It was an ambition," Koller said, "which, through a concurrence of circumstances, I never realized."

Failing to get the appointment, he went to Holland as assistant in the Utrecht Eye Hospital for more training. In 1888, at the end of his term, he looked for a place to start practice for himself, a place where opportunity might await a man willing to work. He selected New York City.

Long before Carl Koller came to the United States, enterprising American doctors were finding that remarkable things could be done with cocaine. They had started to study this drug within a few weeks of the first report at Heidelberg, and within a few months they were making their own discoveries.

In South Norwalk, Connecticut, a German farmer was cleaning a revolver when it went off and shot a bullet into his hand. He waited a day for the bullet to fall out, but the hand only became swollen and painful. Dr. W. C. Burke, Jr., looked at the injury, excused himself for a moment while he thumbed through a medical journal and read a few paragraphs, and then injected a cocaine solution in the *nerve trunk* that sent off branches to the injured part of the hand.

"After waiting five minutes," he reported, "I made the necessary incision, an inch and a half long and quite deep. No pain whatsoever."

Dr. Burke had discovered an important trick in local anesthesia —injection of the drug into a nerve trunk where pain messages would be blocked.

A few days later, R. J. Hall and William Stewart Halsted of New York discovered the same technique for themselves. They injected cocaine into a nerve high up on the leg and found that the whole foot was made numb. Dr. Hall marked another milestone when he also reported, "This afternoon, having to have my tooth filled and finding that the dentine was extremely sensitive, I induced Dr. Nash of 31 West 31st Street to try the effects of cocaine. . . ."

Local anesthesia had entered dentistry.

Also in New York, Leonard Corning made two discoveries that were tremendously significant to the growing field of local anesthesia.

First, almost from idle curiosity, he injected a dose of cocaine into his arm and discovered that the anesthesia lasted for about twenty minutes. Later, he injected the same dose but wrapped a tight bandage just above the site of injection. To his surprise, the numbness lasted for nearly five hours!

Later, he inaugurated a brand-new type of anesthesia. He began a series of experiments ". . . with a view to determining whether the local anesthetization of the spinal cord was within range of practical achievement." Between the crevices of a dog's vertebrae, he injected a few drops of cocaine solution; in a few minutes, the entire rear end of the animal—hind legs, buttocks, tail, and thighs—was completely insensitive.

"Be the destiny of the observation what it may, it has seemed to me, on the whole, worth recording," he wrote.

The destiny of that observation was the development of spinal anesthesia.

VI

During these months when cocaine anesthesia was hailed as one of the greatest discoveries in the memory of man, a terrible shadow was creeping over Europe and America.

Koller's findings had added one more advertising phrase to the long list already dangling from cocaine. In the 1880's, it was being used more than ever before to cure nervous exhaustion, tuberculosis, syphilis, seasickness, anemia, and all the other ills. The sale of Mariani's coca wine was flourishing, and Mariani, himself, was honored by the Pope as a benefactor of humanity. Americans were especially fond of cocaine—hadn't it prolonged the life of former President U. S. Grant for at least four months?

Warnings of the storm on the horizon came from the blatant American newspapers. They splashed stories on their front pages that horrified good conservative medical men. What did those dastardly reporters mean by "cocaine addiction"? Why, everyone knew that cocaine *cured* addiction! It was just what might be expected of the press, frightening and deluding the public to make a good story. There should be laws!

Manufacturer Mariani in Paris warned his patrons to disregard this "newspaper hysteria."

The president of the British Medical Association, Sir Robert Christison, assured his colleagues that it was all a lot of balderdash. "I simply cannot understand these claims of danger," he asserted.

Dr. Sigmund Freud spoke: "I can assure you that cocaine is absolutely harmless, even in long use. It has the highest recommendations for the treatment of indigestion. It is an absolute antidote for morphine addiction. Why, with cocaine in our hands, we can dispense entirely with asylums for addicts!"

One night in New York City, W. A. Hammond appeared before the Neurological Society to quash these idle rumors once and for all. "There have recently been some very striking stories in the newspapers," he said, "regarding the injurious effects of cocaine

upon persons who have become addicted to its use. In order to determine whether there was any truth in these statements, I have made some experiments on myself.

"On four different days, I gave myself an injection. And, gentlemen, I experienced none of those horrible effects," he laughed indulgently, "no disposition to acts of violence whatsoever; why, I didn't even want to commit a murder!" Here he and his audience roared at such wit.

"Furthermore," he continued, "I acquired no habit; I could quit its use at once. Frankly, I consider the cocaine habit, if there is such a thing, to be like the tea or coffee habit. I do not believe there is a single instance of a well-pronounced cocaine addiction with the patient's being unable to stop at any moment he chooses to do so."

These telling blows were greeted with more laughter and applause. That was ticking off the yellow journalists! Then—

"Mr. Chairman, may I have the floor?"

Heads turned as J. B. Mattison of Brooklyn rose to his feet. "Mr. Chairman, I cannot agree with Dr. Hammond. I want to tell you right now that, in the past few months, I have had five cocaine addicts coming to me for treatment!"

The chairman scowled. "Any other comments?"

Leonard Corning, the founder of spinal anesthesia, arose and mentioned that "there is a morbid fear of cocaine spreading through the country." The remarks of Dr. Hammond, he thought, were timely and beneficial, since they would tend to stop this prejudice against a most useful remedy.

Hammond was permitted to terminate the discussion. Smiling at Corning and glaring at Mattison, he said, "I do not deny the existence of a cocaine habit; I claim that the patient can stop it at will."

The general feeling was that Mattison and his fears of cocaine had run into a brick wall. Nevertheless, in the next few months, he stubbornly continued to lead a small group of fighters against the use of cocaine. His group was sincere—Alexander Shaw of Saint Louis, Orpheus Everts of Cincinnati, Daniel Brower of

Chicago, and Albrecht Erlenmeyer in Germany—but against the ridicule, lassitude, and indifference of their foes, the struggle appeared hopeless. It seemed actually impossible to convince the medical profession that it took more than a finger-snap to break the cocaine habit.

The tragic, dramatic denouement came without warning. At a medical meeting in New York, Dr. Frank Ring was discussing cocaine addiction. "I suppose all you men remember Dr. Hammond's talk last year," he began. "You know he gave himself four injections of cocaine and didn't become addicted.

"Well, I've found out why he didn't get the habit. Four injections aren't enough. He should have continued taking cocaine, day after day, for months. He should have kept right on until he liked it, until he looked forward to it every day, until he couldn't wait till he had his dose.

"When he reached that point, he would have had the habit, all right. He wouldn't have come here to tell you men that you can stop it whenever you want to.

"No, he wouldn't have come, then. He'd have had more sense. But I haven't any sense. . . . I've come to tell you what it's like. And before God, gentlemen, I *know!*

"I am a cocaine addict—and I cannot stop!"

VII

Dr. Ring's shocking confession quickly brought to an end all the bickering and argument about the dangers of cocaine. Although he finally succeeded in breaking himself of the cocaine habit, his announcement was never forgotten. Thoroughly aroused to the dangers of cocaine, scientists turned to a new hunt. "There must be other chemicals which can act as local anesthetics," they said. "Perhaps one of these might be safer than cocaine. Where can we find it?"

The search led first to a closer examination of the coca leaf and to studies of other plants and shrubs, but it seemed that nature held

no answer to the question; so the chemists turned to a remarkable compound, phenol, or carbolic acid. This chemical had two distinctive characteristics: it destroyed tissue, and it deadened pain. The scientists set about the job of modifying its formula in order that the tissue destruction could be stopped and the pain-deadening retained. From their labors came a dozen new local anesthetics, all cousins of phenol, which the chemists called amino-hydroxy-benzoic acids—anesthetics such as *orthoform, new orthoform, nirvanin, anesthesin, stovaine, alypin,* and finally *novocaine.*

Novocaine, developed by the German chemist, Albert Einhorn, was the best of the list. Its discovery was one of the first twentieth-century triumphs that made Germans the world's miracle men of chemistry.

In the case of novocaine, however, the Germans kept the honor but not all the profit. At its entrance into the World War in 1916, America took over all German patents, including the one on novocaine, and officially dubbed the drug *procaine.*

Today, novocaine has all but ousted cocaine from modern medicine. Novocaine surpasses cocaine for producing every type of local anesthesia but one—anesthesia of the surface of the eye—and even for this task, cocaine is rarely used. Instead, doctors turn to *butyn,* a synthetic anesthetic developed by Chicago scientists.

While chemists (usually with the aid of their patent attorneys) were discovering new local anesthetics, physicians were learning new ways to use them. In Leipzig one day, Dr. Heinrich Braun, who officially introduced novocaine into medical circles, ran across the old report by Dr. Leonard Corning of New York. "When I wrapped a tight bandage just above the site of the injection," Dr. Corning had reported, "the anesthesia lasted nearly five hours."

"Prolonged anesthesia!" muttered Dr. Braun. "That's just what we need, something to make the numbness last. Yet bandages . . . imagine wrapping a tight bandage about the throat for a tooth extraction! If only there were some other way!"

What did the bandage do, anyway? Braun realized it could have done only one thing—it must have squeezed the blood

vessels so tight that the cocaine couldn't escape, so tight that the anesthetic had to stay right where it was injected and continue to paralyze the nerves.

If this were true, he wondered, what else might do the same thing? He thought of a hundred possibilities, most of them ridiculous and completely impossible substitutes for a simple bandage. And then he thought of *adrenalin*. Adrenalin made blood vessels clamp down on themselves, constricting them until no blood could flow through. It might work just like Dr. Corning's bandage.

Next day in the clinic, Dr. Braun examined a patient whose neck was covered with a mass of boils. "We've got to open those," he remarked, "and we've got to keep his neck numb for at least an hour to do the job. Well, let's see what adrenalin can do."

Into the patient's neck he injected a clear solution of cocaine mixed with adrenalin, and then he began to lance boils. He opened two, three, four—no pain—eight, nine, ten—still no pain—fourteen, fifteen, sixteen—and *still no pain!* He looked at his watch. One hour and ten minutes had elapsed, and the patient was still perfectly comfortable. The anesthetic by itself couldn't have done that, for it would have quickly seeped away from the site of injection and been carried off in the blood. The adrenalin worked that miracle, and local anesthesia made a tremendous stride toward perfection.

The year 1923 saw another admirable advance marked up against pain when a new general anesthetic made its formal bow to medicine at Chicago's Presbyterian Hospital. Many years before, Dr. Arno Luckhardt of the University of Chicago had started to investigate a strange asphyxiation that was attacking carnation plants in a university greenhouse. The guilty gas was isolated and identified as *ethylene*. It was apparently horrible stuff and killed off plants in the twinkling of an eye. Dr. Luckhardt was intrigued to know what ethylene would do to animals.

It should have killed them at the first whiff, but strangely enough it merely put them to sleep—it anesthetized them. More tests showed that it anesthetized them safely; so a few weeks later,

the Chicago scientist submitted himself to ethylene vapor while a select audience of surgeons, physicians, and professional anesthetists watched in wonder. A few days after that, the gas was being used regularly for hospital surgery.

Within a few years, another general anesthetic came from the Toronto laboratory of Henderson and Lucas. This was *cyclopropane.*

In 1930 Dr. Chauncey Leake of the University of California sat down deliberately to design a new painkiller. This was to be no chance discovery but the actual creation of a new drug to do a specific job. "This new compound," he reasoned, "must have such and such an effect. Therefore, it should have such and such a formula. . . ."

Following his chemical blueprint, he produced *divinyl oxide,* a cross between ordinary ether and the newly discovered ethylene. It turned out to be the fastest general anesthetic ever discovered, amazing in its ability to produce anesthesia in a few seconds. For short, quick operations when the surgeon wants anesthesia in a hurry, anesthesia that will last only a few minutes, divinyl oxide appears to be unsurpassed.

By 1947, physicians and researchers could look back on a remarkable chapter in the battle against pain, a hundred years in which they had made great advances—ether and nitrous oxide and chloroform, cocaine and cyclopropane and pentothal and many another. But the battle was not yet over, and the victory was not yet complete. There was still needless pain and suffering in the world. There was still work to be done.

CHAPTER V

Kill the Germs!

LISTER TO EHRLICH TO 205

DURING the reign of Louis XIV, a young Dutchman came to Paris, dropped his real name of Schweitzer, adopted the more dignified title of Jean Adrian Helvetius, and tried to foist on the Parisian public a whole arsenal of panaceas invented by his father, who, it must be admitted, was a quack and not even a good one.

To learn a little about medicine, young Helvetius traveled around the city as an apprentice to Dr. Afforty, studying gout and dropsy and the pox, and Helvetius learned quickly—much more quickly than good Dr. Afforty imagined.

One day the two men, master and apprentice, called on a merchant named Garnier, an importer of rare goods from the New World. Poor M. Garnier was a very sick man, and Dr. Afforty promptly made him even sicker by bleeding him. The Garnier constitution must have been strong, for the patient survived both the disease and the treatment. He paid his bill to the doctor, and in addition offered a little bonus—"a packet of bark, just now received from friends in Brazil, who say it is much prized by the native doctors there."

Dr. Afforty politely refused the present, but not Helvetius—not this smart son of a quack who knew what the public wanted. Helvetius accepted the packet. No one suspected what it might cure, if anything, but he tried to find out, administering it surreptitiously to anyone who would swallow it, anyone suffering from malaria or smallpox, typhus or indigestion, dropsy or headache,

dizziness or hemorrhage. Dr. Afforty didn't know about these sly experiments, but what the doctor didn't know . . .

Finally the Dutch apprentice tried his bark on a patient suffering from violent dysentery. The dysentery stopped. Then on another dysenteric patient and another and another, and each time the drug banished the disease like magic. "This," crowed Helvetius, "is better than any cure I learned from my father. This works!"

Soon Parisians awoke to discover blatant sign-cards posted on their street corners, cards advertising a great Dr. Helvetius and a great cure ("newly arrived from the New World") for dysentery, diarrhea, and sundry disturbances of the bowels. Thousands of Parisians were suffering from dysentery, and the young doctor gave his remedy to all who asked—and paid—for it; but its identity remained a dark secret. Naturally, if everybody knew that dysentery could be cured by powdered bark of the Brazilian ipecacuanha root, how would Helvetius profit?

Eventually Helvetius was mentioned in the palace of the king. The heir to the throne was vilely stricken with dysentery, and the court physician, D'Aquin, brought Helvetius to work a miracle. The miracle was duly wrought, the noble patient cured, and King Louis desired to give this lifesaving drug to the world.

D'Aquin and the king's confessor, Père de la Chaise, called on Helvetius; they discussed the weather, the crops, the state of affairs in current theology, and then slowly but surely approached the subject of the mysterious drug. Helvetius came out of the conference with a thousand louis d'or and appointments as Inspector General of the Hospitals of Flanders and physician to the Duke of Orleans.

The merchant Garnier promptly brought suit for the reward, but Helvetius successfully defended his rights.

King Louis got the secret of the South American plant from this bargain. It was an important bargain, for ipecacuanha, now shortened to *ipecac,* was a valuable specific against dysentery; but this wasn't all—the bargain with Helvetius was also important because of the precedent it set.

Other European rulers now felt a royal obligation to purchase virtually every secret remedy that was waved beneath their noses. Most of these drugs were utterly worthless, but there were a few that justified all the expense. There was Peruvian bark for malaria, purchased by this same Louis XIV; and in 1776, Louis XVI spent eighteen thousand livres to buy the secret of the male-fern cure for hookworm. At that point, medical history swooped around a corner.

Louis XVI hadn't wanted to purchase this drug. He wasn't interested in hookworm, which wasn't very serious in France; but if his illustrious ancestor could buy secret drugs, then so could he. Most European physicians shared the king's lack of enthusiasm for the new cure. They were worrying more about tuberculosis, diphtheria, and typhus, and it was difficult for them to realize that these hookworms, roundworms, tapeworms, and all the other intestinal parasites were important, serious, and even deadly.

Indeed, very few Europeans could comprehend that the worm diseases were man's deadly enemies in the tropics, infesting and weakening and often helping to kill *hundreds of millions of people!* No, the European medical men didn't realize all that. But when they saw how this new drug cured their few hookworm victims, they opened their eyes to a more significant discovery.

"Observe how this medicine works!" they exclaimed. "See, it exorcises worms from the intestines, big worms that can't be missed. Surely, then, these worms are the *cause* of the disease, for when the worms depart, the patient becomes well again."

Soon these doctors began having even stranger thoughts. "If there are big worms which we can see, maybe there are also little worms too small to be visible. Maybe these tiny worms can also cause disease. And if some drugs can kill the big worms, maybe there are other drugs that will kill the little ones. . . ."

In France, there was a sickly little chemist who was wondering about that. His name was Louis Pasteur. There was an explosive young Parisian pharmacist, Jules Lemaire, and an almost insane Hungarian obstetrician, Ignaz Semmelweiss, who struggled to put

his thoughts into words. There was the kind, witty American doctor, Oliver Wendell Holmes, who wrote so easily.

And just arriving in Glasgow in 1860 there was a quiet, brilliant Quaker surgeon, young Dr. Joseph Lister. . . .

II

Surgery in 1860 was a gory business. Few surgeons dared do much besides take care of broken bones, skin tumors, and simple accidental injuries. The man who attempted anything more, anything as unthinkable as an abdominal operation, ran the risk of being forever labeled a murderous fool.

Few patients let themselves be put under the knife, and most hospitals could do a week's surgery comfortably on a Wednesday afternoon.

In the operating rooms, surgeons worked in their bloody frock coats, wiped knives on their cuffs, and sewed wounds together with dirty silk thread pulled out of their pockets.

The most common operation was amputation of a limb, usually performed in a valiant attempt to save life after a compound fracture (with the broken bone sticking out through the skin) had become putrefied. Amputations were considered reasonably safe; one London surgeon boasted he lost only one case in each four and pointed to mortality rates of 26 per cent in Massachusetts, 43 per cent at Edinburgh, 46 per cent at Zurich, and 60 per cent—six deaths out of ten—at Paris.

In the wards, sweltering in an atmosphere of perpetual fetid odors, patients sickened and died from blood poisoning, tetanus, gangrene, erysipelas, and a host of other indescribably ghastly diseases which followed the simplest operations. The operations weren't so bad—it was the terrible "hospital disease" afterward that made the patients certain they would have been much better off in the gutter.

A few doctors tried to stop this carnage; and in their blind, stumbling way they recommended more and better ventilation of

the wards, use of lye on the walls, and often the complete abandonment of certain accursed hospitals.

In one hospital each year, the chief surgeon used to post a sign: "This is the season when erysipelas prevails in the wards; we will do no more operations until the first of March."

At Saint Thomas' Hospital in London, there was a faded notice in the dissecting room where students worked on dead, putrefying bodies: "Gentlemen who are dissecting or doing post-mortem work should wash their hands in chlorinated soda solution before going to their patients." But nobody ever bothered about such a silly business, and even if one had wanted to follow the directions, there was no "chlorinated soda solution" to be found.

In Budapest, wild-eyed Ignaz Semmelweiss tried in vain to convince the medical world that these hospital diseases could be blamed on the doctors themselves—that in their ward rounds they carried diseased, putrid matter from one patient to another.

But most surgeons bowed before the fate of their profession and rationalized that the postoperative horror was unavoidable. "Get rid of pus? Oh, but that's quite undesirable! After all, pus is necessary to make the wound heal."

So in 1860, young Dr. Lister came to Glasgow to be professor of surgery at the University. For four years he battled the hospital disease that raged through his wards. For four years he made his nurses and his house surgeons wash their hands frequently. ("The silly ass! We'll just get 'em bloody again. . . .") For four years he fought with his Scotch board of directors for more clean towels, for more fresh dressings on pus-infected wounds, for more gallons of deodorants.

Then one fateful day in the autumn of 1864, Lister walked home with his fellow professor, Thomas Anderson, the chemist.

"I say, Lister," asked Anderson, "what do you think of this chap, Louis Pasteur?"

"Pasteur? Louis Pasteur?" Lister fingered his silky sideburns. "I'm afraid I don't recall the name. A Frenchman, I presume?"

"Indeed, yes, and a very remarkable Frenchman. Don't know

him personally, but I've been reading his articles in the *Comptes rendus*. Striking thing he's doing, with bacteria. Claims they're responsible for putrefaction and fermentation."

"That's an interesting thought. Bacteria, eh?"

"Yes, bacteria and other microbes. They might, you know, be responsible for the wound putrefaction and pus formation which worry you surgical fellows. . . ."

Lister went home and thought about that. Furthermore, for this quiet Quaker was a very ferret of a man, he went to the library and read Pasteur's articles in the French journals. "This is most extraordinary," he thought. "With what he's already found in his experiments . . . I wonder, could these microbes cause disease? It is almost unthinkable, but perhaps . . ."

Lister became, for a while, a microbe-hunter. He repeated some of Pasteur's quixotic experiments and found, as had Pasteur, that when there were no microbes, there was no putrefaction.

Lister then became a microbe-killer. He was convinced now that his hospital diseases, the terrible cases of blood poisoning and gangrene, must be caused by microbes—*microbes that got into the body when the skin was cut open.*

There must be some way to keep these germs out, to kill them. He referred again to Pasteur's reports, but the Frenchman was interested only in fermenting wines and sugar solutions and fluids; he could kill microbes in these liquids by boiling them. But you can't boil a patient.

Lister consulted the professor of chemistry again. "Anderson," he said, "I'm looking for something that will kill microbes—something besides heat. I want a chemical, perhaps, some benign substance that I can apply safely to the living body. What can you suggest?"

"Well," offered Anderson, "there are really a number of chemicals like that, antiseptics that stop putrefaction. There are alcohol and glycerin, of course; and salt and chloride of lime; benzoin and some of the vegetable oils. They're all historically old, but not very effective. I really can't . . . Wait! How about phenol?"

Lister was puzzled. "And what is phenol?"

"Oh, it's the same as carbolic acid. It's an extract of coal tar, and you know what coal tar does."

"Frankly, no, I don't."

"Of course, you're not a chemist! Well, coal and pitch and coal tar have been used for centuries. Egyptians probably used 'em to preserve their mummies. We use it now to preserve ship's wood and railroad ties. Utterly stops rot and decay. That ought to kill your microbes."

"Perhaps," remarked Lister. "Perhaps it ought. Thank you, Anderson, I shall think about it. And if I should want some of this phenol or carbolic acid or whatever you call it?"

"There's a chap I know in Manchester, Freddy Calvert. He's starting to extract phenol on a small scale now."

Lister gave the matter still more thought. The horrible and, he was sure, needless deaths from hospital disease had weighed heavily on his sensitive soul; yet he wanted to be very, very sure before trying any radical treatments. After all, no one had proved that microbes actually did cause disease.

Only a few weeks later, Mrs. Lister called his attention to a short article in the newspaper. "Joseph," she remarked, "here's something about that carbolic acid you mentioned to us. It says that a Dr. Crookes used it at the sewage works in Carlisle."

"Eh? What else does it say?"

"Well, it says that the carbolic acid stopped the strong odor due to putrefaction of the sewage. Joseph, how did that happen?"

"Undoubtedly it killed the microbes that are responsible for the putrefaction."

"Killed the microbes, Joseph? Are microbes really so bad they cause unpleasant odors?"

"My dear," replied Lister, "they are probably much worse than that. They may also, I suspect, cause disease in human beings. They . . . by the way, what was that man's name? Was it Calvert? Yes, I must write him in the morning. Hm-mm, so carbolic acid can stop putrefaction in sewage. . . ."

When the shipment of carbolic acid arrived from Manchester, the Glasgow surgeon was hardly impressed. It was a dark, tarry, malodorous fluid, scarcely the sort of thing to inspire confidence in its ability to assassinate germs. But Lister didn't know, since he had little time to read scientific journals, that this phenol or carbolic acid was one of the most potent germ-killers in the world.

He didn't know that German chemists had found it would stop putrefaction in a few seconds. He didn't know that French pharmacists and a few doctors were trying to cure disease with dusting powders and healing fluids composed primarily of phenol. And he didn't know that, even in England, this dirty chemical had already been used as an antiseptic during an epidemic of cattle plague.

Lister didn't know all that, and, of the greatest significance, *neither did most of the rest of the world!* Medicine needed someone to discover phenol all over again and really make something of it.

For a few weeks, that rediscovery hung in the balance and was almost never made. Lister had left orders at the hospital that he was to be called in any case of compound fracture. One night he was summoned to treat such a case, but even after the dark liquid was applied, putrefaction of the wound followed, and the patient died. Lister came close to giving up his dream then and there, but he felt that hadn't been a fair test and resolved to try once more.

On the morning of August 12, 1865—a very great day for medicine—he was called to see an eleven-year-old boy whose left leg had been smashed by the wheel of a heavy wooden cart. There was a long gash on the lad's leg, and through this protruded the sharp end of one broken bone.

While house surgeons and assistants watched in horrified amazement—after all, the first patient had died!—the bones were set, and a clean dressing was placed over the wound. The dressing was soaked in full-strength carbolic acid.

The entire surgical staff waited and watched little Jaimie. They

waited for the fever, the pain, the nauseous odor from the wound, and the inevitable appearance of pus.

On the fourth day the dressing was removed. The wound was clean with a good, sound scab forming over it. There was a little reddening—naturally, for it had been soaked with concentrated carbolic acid—but *there was no pus!*

At the end of six weeks Jaimie walked out of the hospital with a repaired leg and not a trace of infection.

For two years, Lister experimented with his magical new liquid. He secured better, purer solutions of phenol. He learned the proper dilutions to prevent infection without unduly damaging the patient. He selected his patients carefully and directed their care like a tyrant; not a few drops of carbolic acid, he ruled, but gallons of it. The microbes must not be given a chance!

After cautious experimenting, he dared the invasion of fields once forbidden to surgeons. He operated on the knee and the ankle—cutting into healthy flesh to repair damaged bones, counting on his precious carbolic acid to protect against infection. He risked an abdominal operation that no other surgeon in England was willing to attempt and performed it successfully—on his sister.

At a meeting of the British Medical Association in Dublin he announced his methods and his results, but won only the jeers and ridicule of his colleagues. "Look here, old man," one surgeon remarked, "your carbolic thingumabob sounds most awfully complicated; I rather prefer bread poultices. . . ."

"Never mind," muttered Lister, "they will learn. They must learn!"

He went back home to experiment on surgical threads and developed catgut (sterilized, of course, by a bath in carbolic acid).

He demonstrated his methods to important visitors from abroad and convinced them. He wrote articles in the medical journals and convinced the Germans, the French, and the Scandinavians, but not the English.

He was called into consultation on one case, found a deep-seated

infection, treated it with carbolic acid, and virtually had to invent sterilized rubber drainage tubes on the spot. They worked wonderfully well and undoubtedly saved the life of his patient—Queen Victoria.

He tried new substitutes for carbolic acid and new ways to apply them, but he always came back to carbolic acid—and lots of it. And the patients blessed him; the terrible odor of putrefaction began to disappear from the surgical wards, the ghastly "hospital diseases" were slowly beaten back, and hospitals were no longer called back doors to the cemetery.

There were opponents, naturally, who battled Listerism—big men like Sir James Simpson, discoverer of chloroform, and little men who made their little howls: "Lister's not original! Other men used phenol first!" (This Lister never denied.) "Antiseptic surgery is a humiliating fad!" "It's a return to the dark days of surgery!" "The antiseptic 'theory' is already in its driveling stage!"

And all over England, particularly in London, the Great Doctors scoffed. "Pasteur and Lister—a pair of blasted dreamers. Doing surgery a lot of damage. Upsetting our patients. Something really should be done. . . ."

But Lister and his boys, the men he had trained and taught, were unimpressed by catcalls and hoots. They were saving lives, and their records proved it. America and most of Europe learned this lesson gracefully; England took it the hard way, but eventually even England took it. Even England had to believe Lister and Pasteur.

There was one criticism of Listerian antiseptics, however, that was more than justified. Carbolic acid was a germ-killer, but it was a devilishly strong chemical. It was cruel to sensitive tissues, and it poisoned hundreds of patients; even surgeons became sick from phenol poisoning—which was hardly surprising with the clouds of carbolic acid vapor that filled every operating room.

Soon there began a search for a safe substitute for phenol, a search that was destined to lead to the most surprising places. On the way, some scientists suggested boric acid and hypochlorite

solutions. An American surgeon recommended iodine. A German suggested the oil from fossilized fish. A Frenchman urged the disgustingly vile-smelling iodoform. Still others proposed potent salts of mercury, sulphites, bromides, chlorides, and a hundred others.

As far as surgery was concerned, the solution came in a startling fashion. In Germany, there arose a new school, the school of non-septic or aseptic surgery. "Don't bother about killing germs *after* they get in," said the Germans. "Don't ever let them get into the body at all!"

So surgery turned to the picturesque new methods of asepsis, of preoperative disinfection. A new breed of surgeons appeared—"the men in white"—who rubbed and scrubbed before going to work; who wore sterilized gowns, sterilized masks, sterilized caps, sterilized gloves, and sterilized shoes; who handled sterilized instruments on sterilized patients lying on sterilized beds in sterilized rooms.

It was pathetically comical to see how Lister's more ebullient disciples, using the very same standpat arguments which had once been hurled against them, turned against this improvement.

But that didn't stop the search. Carbolic acid undeniably killed microbes, and microbes—as Pasteur had definitely proved by now—undeniably caused diseases. Even if surgery could get along without a germ-killer, medicine could not. "All right," said the doctors, "Let's use carbolic acid to cure diseases—let's use it to cure cholera and plague and typhus and pneumonia and blood poisoning!"

No, that was impossible. Carbolic acid is too dangerous to put inside the body.

"Very well, then, what can we use instead?" The doctors turned to the scientists. "What can we use as a substitute germ-killer? What can you recommend that is safe and sure, that we can put inside the body where the germs are at work?"

"We can't recommend anything yet," the scientists sadly reported, "but don't give up hope. We're looking for something. . . ."

III

Paul Ehrlich, who influenced the lives of millions of people, who rescued them from a shameful living death, was himself most influenced by two men.

One was his cousin, Karl Weigert, the lonely, cautious, ascetic pathologist who spent twenty years trying to color nerve fibers so they could be readily seen under a microscope.

The other was Robert Koch, the country doctor who revolutionized the game of microbe-hunting, who discovered the tubercle bacillus and a gang of other murderous microbes, and who gaily ended his spectacular scientific career by a spectacular elopement with a chorus girl.

Koch had been dragged away in 1876 from his tiny country laboratory to become municipal physician in the city of Breslau. He went visiting one day and called at Breslau's medical school, where the dignified and not too cordial professors showed him through their departments. In the pathology laboratory, they pointed out a young student working at a table smeared and gaudy with colors which had spilled from dozens of bottles of dyes.

"There," they said, "is our little Ehrlich. He is a first-rate stainer of tissues, but he will never pass his examinations."

Little Ehrlich never did pass his examinations; he wasn't interested in them. He went from school to school, from Breslau to Strasbourg to Freiburg to Leipzig—leaving behind him desks stained with bright purples and crimsons and yellows and greens, leaving behind professors who shook their heads sadly.

"Ehrlich? Ach, an abominable student. He learned nothing. He memorized nothing. But such beautiful stains and dyes and colors he could mix . . . indeed, he should have been a painter!"

His professors might well have barred him from their classes, which he never attended anyhow, for Ehrlich clearly did not fit the accepted pattern of all good medical students. But there were smart teachers in those days, and they didn't pay too much attention to patterns and standards and grades.

Did the professor of medicine growl because Ehrlich didn't memorize the thousands of drugs he should know? "Come, now," other professors suggested, "go easy on the boy. Maybe, with those messy stains of his, he might make some real discoveries—he might find some way to diagnose diseases or pick out some new tissues or cells." So it was generally decided that if Ehrlich wanted to waste his time coloring thin slices of tissues, if he wanted to learn medicine in his own odd way, that was his business.

It took the young dauber an extra year, but eventually he won his medical degree—not because he finally passed any examinations, but because the professors couldn't overlook the latest results of Ehrlich's staining experiments. In his unorthodox, outlandish research, he had founded a new branch of blood science.

Already the young scientist had discovered *five new kinds of blood cells in the body.*

Paul Ehrlich never consciously admitted that he didn't want to be a baby-pulling, fever-taking, hand-holding doctor; he never bothered to think about such unimportant things. Yet somehow, after his graduation, he landed the job as assistant to the great von Frerichs in the first medical clinic of Berlin's Charité Hospital—today it seems the appointment must have been a case of mistaken identity!—and he stayed there for seven years.

If Ehrlich was a bad medical student, he was a worse doctor. When other staff doctors went off to ward rounds, he stayed behind in his little office and poured green dyes on exquisitely thin slices of liver. When he visited his patients, he left orange and purple stains all over their bedclothes. When he was called to deliver a baby, he was more interested in getting a good snip of tissue from the afterbirth than in the weight, welfare, or sex of the squalling infant.

After seven years of this, even easygoing von Frerichs admitted that enough was enough, and it was arranged that Ehrlich should be transferred to another clinic. Ehrlich didn't mind; after all, why should he, since he could always bring along his dyes, always find a tiny bench where he could stain tissues—and bacteria.

Bacteria! Those little pests really needed staining; they were so small and insignificant that Ehrlich got headaches when he tried to spot them under his microscope. And how could he tell when a tissue was infected unless he could see these bacteria? If, now, he could only find some lovely stain that would so color those infinitely small killers that they would be easy to find—then it would be easy to diagnose an infection or the cause of a death!

١٢ Ehrlich was a hopelessly bad experimenter, careless and sloppy, spilling his dyes—and his bacteria—all over his desk, his notebooks, his room, and his clothes. He spilled everything—blood from a man just dead of typhus fever, bits of tissue from a malignant cancer, sputum from a woman dying of tuberculosis—everything with which he worked.

Perhaps it was one of those accidents that did it; one day Ehrlich discovered he had tuberculosis and went off to Egypt to recover. He failed to realize how sick he was, but many of his colleagues felt sure he would never come back.

If Ehrlich had died there in Egypt, at the age of thirty-three, science would have lost a man who had already become famous, a man who had established the field of blood-cell science, who had discovered new dyes and new ways of dyeing, who had even found a dye to stain the deadly tubercle bacillus which Robert Koch had isolated only five years before—and which was now burrowing in Ehrlich's own lungs.

But Ehrlich did not die in Egypt of tuberculosis. He came back to Germany, not the least bit worried, although he promised his wife to live more carefully from now on—a promise which, somehow, he forgot to remember. He was nearly thirty-five and there was so much work to be done! He came back to Berlin where his wife—who, thank the gods of science, had a little money—established a tiny laboratory for him and bought him the bottles of dyes which were his own life's blood.

Then Robert Koch reappeared, covered with new laurels for his discovery of the comma-shaped bug that causes cholera, the little rod that infects the eyes of Egyptian babies, and the slimy

amoeba which causes dysentery. He was one of the great microbe-hunters, and Germany had built for him an "Institute of Infectious Diseases" in Berlin.

"Come in with me," he invited Paul Ehrlich. "You'll like our men—Gaffky, Loeffler, Pfeiffer, Welch from America, Kitasato from Tokio—but you don't have to work with them. You can have your own laboratory and your own dyes. You can work on anything you like. . . ."

So Ehrlich moved his beloved bottles to Koch's institute and started to work out more dizzy combinations of colors. He also had a few new ideas which had incubated while he was coughing up blood and tubercle bacilli in Egypt. The microbe-hunters were thinking now about immunity, and his cousin Karl Weigert had given him a wondrous new theory—an idea to explain all immunity. Thus, while Koch went off hunting for new microbes and fighting cholera in Hamburg, little Ehrlich stayed in his cubicle and tried to find why animals became immune not merely to the living diphtheria bacillus and anthrax germ but also to such dead chemicals as poison from the castor-oil bean. And he tried a wild new stunt in tissue-dyeing—adding the dyes to living animals.

"Herr Gott!" he would shout. "Look at this. I inject methylene blue into this nice little rat, and it colors all the nerve endings such a beautiful blue. Now, how does that happen, hein? Why does it color *only* the nerve endings?"

Affinity, that's what it must be, an affinity between his beautiful dye and the nerve cells. And, he reasoned, there must be an affinity between other cells and other chemicals, between body cells and chemicals, between *microbe* cells and chemicals. Now, if you could only get an affinity—a chemical love affair—established between some microbe and some microbe-killing chemical . . .

Paul Ehrlich had an idea there, a revolutionary theory (even though it happened to be all wrong), but he didn't have time to get a good grip on it. Dr. Emil von Behring had just discovered an antitoxin to cure diphtheria, but nobody could manufacture this lifesaving preparation. Sometimes it was too strong, and sometimes

it wasn't strong enough. Ehrlich, who didn't think much of von Behring, turned with evil glee to the job of standardizing diphtheria antitoxin.

"That von Behring is a fool!" he muttered. "He makes a lovely discovery and doesn't even know how to use it. Can't measure!"

The government set up a special little laboratory where Ehrlich could go ahead and "measure" this new cure for diphtheria. It was a very little laboratory, a onetime stable, located just outside Berlin in Steglitz. There Ehrlich perfected the production of the diphtheria cure—making it just strong enough and never too strong. Distinguished visitors came from London, Paris, Lisbon, Tokio, and even Washington—for the world had begged for safe protection of its diphtheria-threatened children—and Ehrlich explained his methods, at the same time drawing wild, undecipherable graphs and formulas on any piece of paper that he could reach and making most uncomplimentary remarks about von Behring.

The Steglitz laboratory was much too small, and Ehrlich and his boys, his antitoxins and his dyes, all moved to a new laboratory which was built for him at Frankfort on the Main. That was a lot better, but it still wasn't big enough to let him do much more than standardize antitoxin, and Ehrlich wanted to get back to his dyes. Mrs. Ehrlich came to the rescue again—how Hedwig Ehrlich did help her outlandish husband!—and discovered the wealthy widow of Banker Speyer. Soon, next door to the Frankfort laboratory, there appeared the Georg Speyer Memorial Laboratory.

Meanwhile, Ehrlich and his boys had gone snuffing up the trail of a new and infinitely terrible army of killers, corkscrew germs known as *trypanosomes*.

"These are gorgeous little beasts," Ehrlich told everybody. "They're bigger than most microbes, and you can see them through the microscope without ruining your eyes. They're deadly, too; they kill millions of men and animals. Maybe we can get a dye that can paint them and kill them."

Playing with these trypanosomes was dangerous sport. One of them was the cause of African sleeping sickness. There was another

responsible for the deadly nagana in African horses and cows, and another that produced *mal de caderas*, a strange malady that crippled the hindquarters of South American horses. Against this whole tribe Ehrlich turned the efforts of all his dyes and all his boys. "We've got to find some way to color these germs with a dye," he directed, "and maybe—if we're lucky—we'll find a dye that will kill the little devils."

They were off on a hunt for a germ-killing dye.

There were hundreds of old, well-known dyestuffs to test. There were still more new products which German dye chemists were inventing every day. And in addition to these dyes, there were thousands of other chemicals which Ehrlich collected from all over Germany. And as if these weren't enough, he designed crazy, fiendish formulas for still uncreated chemicals—chemicals that couldn't conceivably be made—and his boys made them.

Out of this nightmare of research came only one dye with any promise of value, a red powder which was called trypan (short for "trypanosome") red. Ehrlich's assistant, the excellent Mr. Shiga, tested trypan red and found it would kill the trypanosomes which caused *mal de caderas*—but it worked only in mice, not in the test tube, and definitely not in the horses which got the disease.

It was the best they could find, and it was virtually useless. Ehrlich was ready to give up, but cousin Karl Weigert in his sad, solemn way urged one more attempt—always one more attempt.

"You say it is impossible, Paul?" he would ask. "But you must try once more, just to please me. I am positive you are on the right path."

In a spasm of temperament, Ehrlich threw books, paced up and down the floor, hurled his cigar out of the window; but he always agreed. Just once more!

While the boys still fussed with the hopeless dyes, Ehrlich found a new inspiration. In an English medical journal he had read a report by two researchers at the Liverpool School of Tropical Medicine. They announced the successful slaughter of sleeping-sickness germs with a powerful arsenic-containing drug known

as *atoxyl.* Then he heard that his friend Koch was testing *atoxyl* in Africa.

Ehrlich didn't think much of the Englishmen, but if Koch was using it . . .

He pulled out of his pocket one of the colored cards he always carried, wrote a note to his incredible chemist, Bertheim. "Make some atoxyl. We will use it on sleeping sickness, nagana, and *mal de caderas.*"

Bertheim rushed up to the Chief. "Herr Geheimrat," he expostulated, "this is impossible!"

"Nonsense, it is not impossible." Ehrlich scowled at the patient chemist. "What makes you think so? A fine chemist like you, you can't make atoxyl?"

"Of course I can make it, Herr Geheimrat, but you can't use it. Do you know what atoxyl does? Didn't you read the Koch report?"

"Ach, I know all that. So Koch says atoxyl produces blindness—is that what you mean? Well, don't you worry about that. You make me some atoxyl, and we'll *fix* it, eh? We'll change it a little tiny bit so it won't hurt anybody's eyes."

But unhappy Bertheim remained unconvinced. "That is also impossible. You can't tamper with atoxyl. It's one of those sensitive compounds that can't be changed!"

"Ah, my dear Bertheim," purred Ehrlich, "but I'm sure *you* can do it."

Determined to get a nonblinding atoxyl if he had to give his life for it, Bertheim went back to his laboratory. He couldn't resist the Chief's "my dear Bertheim."

changed

And Ehrlich was right. Atoxyl could be tampered with—although everyone had denied it—and the once-sceptical Bertheim found that this dangerous arsenic-containing chemical could be changed a hundred ways. It could be hooked up to dyestuffs; it could be made acidic or alkaline. There seemed to be no end to the number of atoxyl derivatives that Bertheim was now able to make; and that merely meant more work for the drug-testers, for each new chemical had to be studied on animals.

Now the mice were killed by the hundreds and thousands. Mice with blood thickened by the little corkscrew trypanosomes which the new compounds couldn't kill—mice killed by the compounds themselves—mice cured but blinded—mice suddenly adopting the quaint custom of dancing and whirling like dervishes.

But this time there was no stopping Paul Ehrlich. Now he knew he had the solution for these trypanosome diseases—all he had to do was try enough arsenic drugs, enough variations of atoxyl. He invented still more impossible compounds, which his long-suffering chemist somehow always made. He ran around to lectures and meetings—arguing and expostulating and explaining to anyone who would listen, drawing his ever-essential diagrams on the floor, on the walls, on the soles of his shoes, on his cuffs and shirt fronts.

At home he wrote scores of directions—always on the colored cards, for Ehrlich loved color—and deposited them on the desks of his assistants the next morning. He wrote notes on the margins of his solitaire cards, across the pages of his books, on old letters and envelopes. He read scientific books by the ton—and remembered what he read—but he forgot to eat and to put on proper clothes; he could never remember where he had left his money; and sometimes he forgot his daughters' names. But never, never did he forget what he read, and never did he forget what his assistants were testing nor what results they obtained.

He smoked his big, vile, imported cigars, fifteen or twenty a day, and drank Seltzer water by the gallon. He let himself be mothered by Martha Marquardt (he never could get used to this efficient secretary) and by Kadereit, the phenomenal ex-army sergeant who was errand-boy, glass-washer, message-taker, chief usher, father confessor, and general laboratory factotum.

Now, in spite of this mad whirl, the boys were getting closer. Early in 1907 they had tried four hundred, five hundred, six hundred and five different compounds on the whirling trypanosomes. And then they tried the six hundred and sixth, a compound that groaned under the name of di-oxy-di-amido-arseno-benzol.

This 606 was another of Ehrlich's impossible inventions, a drug that couldn't be synthesized, but Bertheim had made it. And 606 could work magic—one shot of it into mice wiped out the evil trypanosomes. It cured the mice without blinding them, without wrecking their brains, without doing them any harm. It was wonderful for mice and for sick South American horses. But Ehrlich didn't stop there; he remembered something else he had read.

Another scientist had just written a fantastic paper, claiming that trypanosomes were cousins of an entirely different breed of microbe—of the microbe that caused syphilis. And now, "If my 606 can kill trypanosomes," Ehrlich dreamed, "perhaps it can also kill the microbe of syphilis."

Just at this crucial moment a new drug-tester arrived from Tokio to assist Ehrlich. He was Mr. S. Hata. Ehrlich could work him like a slave, for S. Hata never complained, never tired, never grew careless. And this estimable, wonderful, amazing Japanese knew how to handle the syphilis microbe and how to inoculate it into rabbits and monkeys.

Soon the animal house was filled with rabbits and monkeys placed in Hata's care. Hata patted them, Hata clucked over them, Hata gave them every comfort—but also, and very apologetically, he scarred them with evil ulcers packed with the tiny, terrible syphilis microbes. Little Hata gave the disease to his animals, and then he injected 606—and cured them. For unbelievable as it seemed even to Ehrlich, 606 could cure syphilis.

Now 606 cured syphilis in rabbits and in monkeys, but what about man—what about the men, women, and children who had been cursed with syphilis and who could get no aid from science? Would 606 cure them?

Ehrlich first had to be absolutely sure that 606 was safe. It took two years of backbreaking tests to convince him, and even the never-tiring Hata became a little impatient with the endless tests on mice, rabbits, monkeys, and more mice. In the midst of all this,

Ehrlich learned he had won the Nobel prize—not for his discovery of 606, which had not even been announced—but for his early work on blood cells and dyes and immunological theorizing.

Finally in September, 1909, Paul Ehrlich decided that tests on human beings could be postponed no longer. He sent samples of his drug, carefully sealed in airtight vials, to Conrad Alt at Uchtspringe, to Professor Schreiber at Magdeburg, to other trusted friends at Pavia and Sarajevo. In addition, he sent some of his 606 to Julius Iverson in Saint Petersburg for tests on relapsing fever, a disease caused by a close relative of the syphilis germ.

"Try this on your patients," Ehrlich directed, "and let me have your results at once. Let me know immediately if there are any bad effects. But do not under any condition mention these experiments to anyone. I do not wish to arouse false hopes. . . ."

In April, 1910, the first results were in, and these doctors pressed Ehrlich to make a public announcement. Against his will, he consented to make this announcement before the Congress for Internal Medicine, meeting at Wiesbaden, and the world suddenly became aware of the magician of Frankfort. Very few people had paid attention to the early studies on dyes and blood cells and to Ehrlich's preposterous theories; but here was a man who had cured syphilis, and syphilis was an old and terrible malady.

The world came to Ehrlich and demanded to be cleansed.

Doctors came to the little Frankfort laboratory and begged for supplies of 606, and Ehrlich had to explain that his assistants were working night and day to manufacture it. He answered every request he could, keeping careful records—in pencil, on the back of the cupboard door in his office!—so he could know who was using 606 and how it was working.

Patients came and begged for a cure. From all over the world came letters asking for help and advice, asking for money or jobs, asking if potato flowers could cure cancer, requesting autographs, offering congratulations and blessings. Great dignitaries came, famous physicians and scientists and important officials; to them all Ehrlich tried to be polite and helpful.

There were still others who wrote dreadful letters to the tired, excited little scientist. He was accused of interfering with the "God-given curse of sin." He was reviled for patenting 606, although he tried to explain that he made no money from it, that the patent was to insure production of a safe, reliable drug.

Ehrlich tried desperately hard to explain everything, to make everybody happy, but he knew pathetically little of the world around him and nothing of the uselessness of explanations. Even when he and his boys brought out a still better and safer antisyphilis drug, number 914 or "neosalvarsan," many people were not satisfied.

Paul Ehrlich died in 1915, the most colorful and the most gallant of all the microbe-hunters. At the end, pale and anemic, terribly tired, he was still afraid his work had not been finished.

"If I could only have just a little more time," he asked, "just a little more time . . . there's so much I wanted to do. . . ."

IV

The pace during those last years before Ehrlich's death had been entirely too tempestuous, and the scientists needed time to catch their breaths, to assimilate the lessons that the old master had taught. Then, slowly during the war years and rapidly after 1918, they found time to pick up the threads that Ehrlich left behind.

Ehrlich had proved that even such a poisonous metal as arsenic could be tamed by putting it into a complex chemical compound, and now other workers tried to perform similar conjurings with other poisons. They took mercury salts, hellish compounds which had once been used to treat syphilis, and made mild, useful antiseptics like *metaphen, merthiolate,* and *mercurochrome.* They took that strange metal, antimony, and harnessed it to battle sleeping sickness in Africa, Oriental sore in India, and the terrible kala azar in India, China, and the countries of the Mediterranean.

There were workers who felt that 606 wasn't the only good

arsenic compound, and so Heidelberger, Jacobs, Brown, and Louise Pearce of Rockefeller brought out *tryparsamide* for sleeping sickness and for syphilis of the brain. Ernest Fourneau of the Pasteur Institute developed *stovarsol* for early syphilis. And there was *carbarsone,* left over from the hectic days of Ehrlich and Bertheim and ignored by the Germans because it wouldn't kill trypanosomes; but Leake, Anderson, and Chen at the University of California found that carbarsone would murder sticky amoebae, and they introduced it as the best treatment for amoebic dysentery—unfortunately not quite in time to ward off the outbreak of that "tropical" disease in the very untropical city of Chicago.

There was *mapharsen,* which Ehrlich thought too toxic to be used on syphilitics, but other scientists learned how it could be handled safely and effectively.

And then there were the beautiful dyes, Ehrlich's first and chief love. There was *trypaflavine*—Ehrlich saw no good in it, since it wouldn't kill trypanosomes; but his Scotch student, Carl Browning, found it certainly would kill bacteria and used it by the hundredweight on wounded soldiers.

In America, Professor Treat Johnson and young Frederick Lane of Yale and Veader Leonard of Johns Hopkins followed a clue left by Ehrlich and changed useless resorcinol into very useful *hexylresorcinol.*

The men who fought intestinal parasites introduced *thymol* to battle hookworms in Italy and Puerto Rico and *naphthol* to wipe out these worms in Assam, Natal, India, and Ceylon. Stubborn, painstaking Maurice Hall of the United States Bureau of Animal Industry came upon *carbon tetrachloride* in 1921; within a year, it had been rushed off to the Fiji Islands by Rockefeller scientists and used with brilliant results on fifty thousand worm-ridden patients.

But while Rockefeller men were driving out hookworms, while Americans were developing hexylresorcinol and tryparsamide, while Fourneau was trying to find a better, quicker cure for syphi-

lis, a fantastic rumor was spreading from a laboratory in the German city of Hamburg.

It began as a whisper: "Did you hear about those Germans? *They've found a sure cure for some tropical disease!*"

What was this magic compound? No one knew. Behind the closed doors of Hamburg's Institute of Tropical Medicine, a small army of scientists worked desperately and silently. Each week or two, one of them raced to the Reich Health Department in Berlin or to the big Bayer factory at Elberfeld, but they divulged no information.

Not until the end of 1920 did a single bit of news come from the German laboratory, and this report, although it came second-hand, was accepted as true.

"I have learned," a French chemist reported to a colleague in England, "that the new German drug is being tested as a specific for sleeping sickness."

Sleeping sickness—a sure cure for sleeping sickness? When England's Colonial Office heard this, frantic demands were shot all over Great Britain. "Spare no efforts to ascertain the nature of the new German drug. It is imperative that we take advantage of any improved treatment for sleeping sickness!"

For this was 1920, and the deadly disease was ripping through England's vast African empire and through the colonies which England had taken from her defeated German foes. But the poor English scientists could get no more information and counseled patience.

"Surely," they said, "when the German laboratories have finished their testing, when they are sure their drug is safe and effective, they will make their announcement and tell us what it is."

But the British had made a bad guess. When the announcement finally did come from Germany, it was the most surprising, exasperating, and totally unprecedented report they could have received.

"We have perfected a new drug which, thus far, appears to be

a specific remedy for African sleeping sickness. We have named it Bayer 205, or germanin. At the present time, we are not prepared to announce its formula."

English and French scientists were aghast. *Not announce its formula?* Why, they can't do that—they *must* announce it! But the Germans politely declined; they refused to patent the drug (which would have immediately shown its formula); and they refused to send a single sample outside the German borders.

"It is unthinkable!" fumed the French. "What is this, a return to the Dark Ages? Are they trying to foist a secret remedy on us? It is completely despicable—just what you might expect from the Huns!"

"Look here!" remonstrated the British. "After all, you can't do that! It's not at all the sort of thing scientists are supposed to do. . . ."

But the Germans said nothing and kept to their own business, to their job of testing Bayer 205 on more mice, more monkeys, more horses. They were playing their own game in their own way. When they were finally convinced that Bayer 205 was safe for animals, they dared to try it on a patient—oddly enough, on an Englishman who had come back from Africa—an Englishman dying from sleeping sickness and begging the Hamburg doctors to save his life. He was the first human patient, and his return from Hamburg to England set the English scientists even more on edge, for the fellow had come back completely cured.

The foreign demand for Bayer 205 was now at fever pitch, and quite surprisingly it brought helpful answers from the Germans. "We are now able to send you all of the drug you need," they replied, "*providing* you give us your word of honor not to attempt any analysis on it yourself, not to allow anyone else to attempt any analysis . . ."

If the British doctors had any scruples against working on such a basis, they were unimportant when weighed against the intense need of their patients. The British and later the French, the Belgians, and the Dutch accepted Germany's conditions.

Soon it became perfectly clear what lay behind this unparalleled secrecy. Statements, some of them not too subtle, came crackling from Germany—

"We cannot reveal the formula even in a patent, for now our German industry stands uncertain and unprotected against our ancient enemies, the foreign nations. . . ." (And they made no bones about the fact that they were referring to America's wartime seizure of all German patents.)

Bayer officials themselves said: "We may have made a great financial sacrifice for the elaboration and experimentation of a drug. . . . We cannot now present it to the world. A tragic destiny must have willed that Germany discover Bayer 205, a drug which finds its principal application in the tropical regions of colonies, at the time when we have lost all our colonies."

If any foreigners pricked up their ears at those last words, they didn't have to worry long about their meaning. At a meeting in Hamburg, a speaker arose and gave a clear, blunt explanation:

"Bayer 205 is the key to tropical Africa and consequently the key to all the colonies. The German government must, therefore, be required to safeguard this discovery for Germany. Its value is such that any privilege of a share in it granted to other nations must be made conditional *upon the restoration to Germany of her colonial empire!*"

Foreign newspaper correspondents heard that demand and leapt from their seats. "Wow! It's outright blackmail," they shouted as they pounded out telegraphic leads. "This will burn 'em up back home—GERMANY DEMANDS COLONIES FOR SECRET DRUG!"

Back home the politicians, the statesmen, and the scientists were indeed extremely upset and filled the air with sulphurous comments on Teutonic treachery. Imagine!—withholding a lifesaving cure from ten million people to barter for colonies!

In two laboratories, however, the secret of Bayer 205 began to undergo a different kind of attack. In the splendid workshops of the British Dyestuffs Corporation and in the pharmacology laboratory of the Pasteur Institute in Paris, two groups of crack scientists

went to work to analyze the toughest chemical that had ever been created by man.

They had precious few clues for a start—only the names of the Bayer chemists who had made the drug, the factory information that Bayer 205 contained no arsenic or mercury, and the names of the German doctors who had tested it. Most scientists would have claimed that this was no information at all, that they must first have pounds of the drug to break down and analyze. Pounds of Bayer 205?—the Pasteur group gave thanks that they had acquired (nobody mentioned how) the pathetic amount of *two-thousandths of an ounce!*

And with that, these scientific detectives started on the job of solving a billion-dollar puzzle.

Uncanny Ernest Fourneau, head of the Pasteur team, turned up the first real clue. "We must go back," he said, "and find out what these Bayer chemists were doing before the war. What were they patenting then?"

Smart patent experts started wading through the thousands of German chemical patents dating back to 1916, 1914, 1912, and even 1910, and one of them turned up something significant. "Here's one," he reported. "In 1914, one of our German friends took out a patent on some urea derivatives and even claimed they're effective against sleeping sickness."

That was Clue Number One—the suspicion that Bayer 205, too, might be a urea derivative.

Then the British, also checking back on patents, turned up a few more leads which boiled down to Clue Number Two—"It is probably formed of chains of amino-benzoyl radicals, united by amide linkages, with a central urea linkage, and terminal naphthylamine sulphonic acid groups."

Such jargon! But the organic chemists knew what those words meant and translated them into diagrams of chemical formulas. And these men began to get a clearer and clearer picture of the sort of structure Bayer 205 might have.

Gradually they went on to put more and more clues together,

eliminating the thousands of compounds that Bayer 205 could not be, and setting off a few hundred that Bayer 205 might be. Those hundreds went through more eliminations, were cut down to one hundred, to fifty, to twenty-five.

These eliminations had been made on theory alone, on the basis of computations and discussions and arguments and guesses. But those last twenty-five couldn't be cut down by any more armchair research. On the basis of theory, any one of them might be 205. They had to be made and tested.

So the synthesizing chemists went to work, creating each one of the twenty-five chemicals that Bayer 205 might be. Each was a fearfully complex substance, difficult to depict and close to impossible to make, but these men were real chemists (Paul Ehrlich would have relished the way they started by saying "Impossible!" and finished with "Well, we did it.").

Here, then, were twenty-five chemicals—no longer diagrams on a piece of paper but solid powders that could be picked up, rubbed, felt, tasted, weighed. But was one of them Bayer 205? No chemist could answer that question, and the drug-testers moved in.

This new crew had the exacting assignment of testing the chemicals on animals and on the corkscrew germs that cause sleeping sickness. At each step they compared notes with the exasperatingly few details published by the Germans.

Here was chemical #6—it killed the microbes all right, but was much too deadly on animals. It couldn't be Bayer 205.

Here was #11—it was safe on animals, but it couldn't kill the germs. It couldn't be 205.

Here was #24—it was safe and it also killed the germs, but it didn't kill the germs so well as 205. So it couldn't be 205.

Here was #18—it was safe and effective, but too unstable, going bad in the presence of air. It couldn't be 205.

Finally one of the research teams, Fourneau's at the Pasteur Institute, with the British workers only a microbe's eyelash behind them, came to the end of the hunt. There was one chemical that was safe—no safer and no deadlier than Bayer 205; it was effective

—no better and no worse than 205. This one, labeled *Fourneau 309*, was finally compared chemically with the tiny bit of Bayer 205 that had somehow been brought into the laboratory.

Both chemicals had the same melting point, the same yellow-pink color, the same molecular weight. Both acted the same way on germs and on animals. Chemically and medically, it appeared, Bayer 205 and Fourneau 309 were identical.

At first, Germany refused to admit the identity; that turned out to be foolish, for it enabled Fourneau to go ahead and patent his drug in England and America. Finally even the Germans broke down and admitted that Fourneau had performed this veritable miracle, though some of them insinuated that he had lured a disgruntled chemist from the Bayer factory to do it for him.

That Bayer 205–Fourneau 309 job was a real triumph in many ways. Although the drug still hasn't wiped out all sleeping sickness, the whole story taught a vital lesson to scientists—and to statesmen.

You can't withhold any secret preparation very long in these days of intense scientific research.

You can't set off science, put it in a corner, and figure that it won't affect all the little plans of statesmen and politicians.

And you can't make a Frenchman mad, a brilliant Frenchman like Ernest Fourneau, and hope to get away with it.

CHAPTER VI

The Fever-Fighters

KOLBE TO ASPIRIN

"MEDICAL men," announced chemist Hermann Kolbe, "are without exception a lot of muddlers."

"Including me?" asked surgeon Karl Thiersch.

"You? Yah, even you, my friend."

"But why, Hermann?"

Kolbe sniffed sourly. "I tell you why. Look at that crazy fool Pasteur in France. If one of my students couldn't do better work than that fellow, I'd throw him out of my laboratory!"

"Oh. Any other reasons?"

Kolbe sniffed again. "Consider the case of your fine friend, Lister. Just look how he handles carbolic acid—it's an act of God he doesn't kill himself and everybody else."

Dr. Thiersch considered the case very carefully. "Maybe you're right," he admitted. "Pasteur and Lister—they both make mistakes once in a while. But they also do a lot of good. They're going to save many, many lives."

"Ach, nonsense! How can a man do good when all the time he makes mistakes? Do I make mistakes? Never! Never in my whole life have I made a mistake!"

"Um-mm," said Dr. Thiersch.

"Furthermore," Kolbe continued, "I despise people who make mistakes!"

"If I didn't know you so well," remarked the surgeon, "I might feel insulted and walk out. But I came here to get some advice on carbolic acid. Some chemical information."

"Chemical information? That is different, Karl. What can I do for you?" His eyes twinkled in good humor again. "I assure you, I withdraw all my insults."

"This is serious, Hermann. I want to try treating some of my patients with carbolic acid—use it internally on typhus and tuberculosis and croup—but that acid is too dangerous. Is there any other chemical I can use in its place—a chemical that can slowly turn into carbolic acid inside the body?"

"Is there? You've certainly come to the right man! There is, indeed, such a compound, and I am the chemist who discovered how to make it. It is salicylic acid!"

"Really?"

"Of course. Twenty years ago I did it. I discovered a way to synthesize salicylic acid out of carbolic acid, and then I discovered that salicylic acid slowly breaks down in the test tube to form carbolic acid all over again."

"That's wonderful!" Thiersch exclaimed. "But are you sure that salicylic acid will also turn into carbolic acid in the body?"

"Certainly it will. What is the body but a big test tube? I tell you what I will do. Tomorrow the boys start making salicylic acid, and then we will test it for you right away."

"That's good of you. But Hermann . . ."

"Yes?"

"Don't make any mistakes!"

"Me?" said the chemist. "Don't be ridiculous!"

The next morning at an extraordinary early hour, Professor Kolbe trotted into his laboratory at the University of Leipzig, past the laboratory desks, past his startled students, into his office. Then, through the open door, he uttered orders with staccato sharpness.

"Otto, some carbolic acid! Frederick, set up a carbon dioxide generator! You, Ludwig, get the new bottle of caustic soda!"

Within half an hour, Kolbe was ready to start an experiment that would credit this rabid mistake-hater with making one of the worst mistakes in chemical history—a mistake that would open an entire new field of disease to medical conquest.

"Look here," he said to his assistants, "I'm going to repeat a little experiment I made years ago at Marburg. Otto, please, the cork! We're going to make some salicylic acid—pass me the tubing, Ludwig—and we're going to kill microbes. You hear that, boys? We're going to cure every disease in the world. From now on, we're all going to be germ-killers!"

"But, Herr Professor," protested the assistants, "we are chemists. We don't know how to kill germs. How do we start?"

Kolbe looked at them slyly. "Start?—ach, we're nearly finished! Indeed, while you young men sleep at night, I stay awake to think. While you play and drink your beer and sing your songs, I, your professor, always think."

The assistants looked at each other, shrugged their shoulders. Ludwig said, "Herr Professor, while we were—well, drinking our beer, what did you think?"

"I thought," said Kolbe, "that we would make some salicylic acid, and with that salicylic acid we would kill germs."

"But . . ."

"Please! Have the courtesy not to disagree! You were going to ask why salicylic acid should kill germs? I will tell you—because salicylic acid will slowly turn into carbolic acid, and carbolic acid will do the actual killings."

"But why not use carbolic in the first place?"

Kolbe smote his forehead. "Ach, such assistants I have! Because carbolic is too dangerous, and salicylic is perfectly safe. If you get a case of cholera, all you have to do is drink a nice solution of salicylic acid—which is perfectly safe—and it will cure you, just like that!"

All this, the old chemist told his assistants, was good, sound theory and should be perfectly simple to test; so the students in his Leipzig laboratory found themselves transformed into microbe-hunters without further ado. Their first assignment, making shining heaps of salicylic acid crystals, was easy enough for these well-trained chemists; but the job of testing its effects on bugs and germs and microbes—ah, that was another story. These men were totally

unschooled in the finer points of testing a germ-killer. They cluttered up the laboratory with smelly jars of decaying meat and fermenting milk. They fished clumsily for microscopic bugs, let fermentation flasks overflow in the incubator, gagged at the odor of putrid flesh. They tried to keep mold out of the good light beer of Leipzig; they tried to kill harmless yeasts and deadly microscopic assassins from the bodies of dead men.

Always Professor Kolbe stood over them, no longer permitting sarcastic jibes to hide his growing enthusiasm.

"You say, boy, that ordinary milk goes bad in three days, but if you add salicylic acid it remains fresh for a week? Good, good! The salicylic acid must have done the preserving, it must have killed the milk microbes by releasing carbolic acid!" And he would scrawl notes on the scraps of paper that always filled his pockets.

"So salicylic acid prevented this meat from decaying for a month? Good, Otto, good!"

"Did you find that salicylic acid keeps this wine from turning sour, Ludwig? Excellent, my boy, excellent!"

There were months of this work, of this wild, careless, crazy experimenting. Kolbe and his boys performed hundreds of tests that were shockingly inaccurate, tests that, if they had been done by anyone else, would have met with Kolbe's blistering scorn. But he was trying to prove a theory.

Through the winter of 1873 and the spring of 1874, the Leipzig laboratory reeked with the nauseous smell of these strange experiments. Notebooks bulged with the results. The laboratory assistants began to feel a quaint blood brotherhood with all sorts of microbes. Finally Kolbe was satisfied.

"Karl," he reported to his friend Dr. Thiersch, "we are ready to talk business, medical business. Here," he laid out the piles of results, "we have proved what salicylic acid can do in the laboratory."

"It works?"

"Splendidly!" beamed Kolbe.

"It kills microbes?"

"By the millions!"

It was surgeon Thiersch's turn to report a week later. "I could hardly believe it," he told Kolbe. "Six days ago I operated on a young fellow, amputated his leg just above the knee. I sprinkled some of your salicylic acid on the stump and then dressed it in bandages soaked with more of it. And today we opened the dressings. The wound was entirely healed!"

The results were excellent but the theory was wrong. Salicylic acid and not the carbolic acid had killed the germs, for there wasn't a bit of carbolic involved. Kolbe, the great chemist, had overlooked the possibility that salicylic acid itself was a germ-killer. And he had failed to realize that, no matter what happened in the test tube, salicylic acid does not break down in the body to form carbolic acid.

"It is so much better than straight carbolic," Thiersch pointed out delightedly, "for it causes so little irritation and damage to the tissues. And sometimes it makes wounds heal amazingly fast."

Salicylic acid soon became internationally famous. Immediately after the first formal announcements, doctors began demanding this new chemical and using it on their patients, for it worked miraculously (in a few cases); and best of all, it was safer than the deadly carbolic acid.

Kolbe had anticipated a real demand for the new acid. Even before the first reports were published, he had arranged with one of his assistants, Frederick von Heyden, to start a little salicylic acid factory in Dresden. He felt confident his job was done—he had discovered the merits of the new chemical and he had established a factory to supply it. Twelve months later, he realized that he hadn't actually completed anything; he had merely opened a door and neglected to look inside.

At first everything was right with salicylic acid and nothing wrong that a little rationalizing couldn't fix. If a patient died from a wound infection, even after the wound had been sprinkled with salicylic acid, the trouble was that the doctor hadn't used enough acid. If a patient died from typhoid fever or typhus or pneumonia,

even after he had been pumped full of salicylic acid—well, treatment hadn't been started soon enough. If a patient complained of too much buzzing or ringing in the ears, that was merely a sign of overdosing.

"Once we get this dosage problem worked out," doctors prophesied, "salicylic acid will be the answer to all infections."

So it was dusted on cuts, surgical wounds, and all kinds of sores and given internally for tuberculosis, rheumatism, dysentery, diphtheria, catarrh, and virtually every other disease that confronted physicians.

If the patient had any kind of sickness, if he were attacked by microbes, the automatic defense was salicylic acid.

Food-manufacturers began to preserve their products with this magic acid, sprinkling it on their meats, mixing it in butter, powdering it into milk.

Optimistic medical reports continued for a year and then slowly changed their tune. All the doctors were agreed on one fact—salicylic acid undoubtedly made their patients feel better—but most of them gradually admitted that the acid cured only those patients who would have survived without any medicine. The usual number of patients were dying of the usual kinds of disease. Typhoid victims, sick, weak, and feverish, reacted beautifully to salicylic acid. A few hours after they swallowed the drug they improved, their fever dropped, and they began to feel like living again. But a few days later they died. The same thing happened with victims of typhus, pneumonia, and all the other diseases.

The explanation of this curious phenomenon came from a young physician in Switzerland. Working in the canton hospital in the city of Saint Gallen, Carl Emil Buss was bothered by this confusion over salicylic acid. His chiefs had told him the drug should act like carbolic acid, killing microbes and curing patients, but his own observations showed this desired result did not actually occur. What did happen, then?

Trying to find out just what salicylic acid really did do, he pored over his record sheets. Here was the case of old Pauline

Strauss—typhoid fever, fourteen days in the hospital, salicylic acid given daily. Within two hours after each treatment, her temperature dropped, and she appeared more comfortable; on the fifteenth day, however, she died.

Here was little Karl Muehlhausen—pneumonia, high fever, salicylic acid given three times. Three times the temperature dropped, but little Karl, too, died.

And here was Johann Bischoff—he had only rheumatism in his joints, but the pain was accompanied by a high fever. Salicylic acid was given, the temperature was reduced, and Bischoff left the hospital, his rheumatism gone. Of course that wasn't important, since nobody dies from rheumatism. But wait a minute . . .

Young Dr. Buss scratched his head and looked back over his notes. It didn't make sense, and perhaps it wasn't very important, but there it was—*if a feverish patient were given salicylic acid, down went his temperature!* No matter what else might happen, no matter whether the patient lived or died, a dose of the acid was invariably followed by decreased fever. Usually the fever came back, but another dose of salicylic acid banished it again.

Now that was utterly ridiculous! Salicylic acid wasn't supposed to be a fever-cure, mused Dr. Buss. Quinine was the only thing that could cure fever—quinine or cold baths or weak, erratic, impractical drugs like alcohol, veratria, aconitia, willow bark . . .

Wait, he thought, willow bark! That's where salicylic acid was first discovered, in *Salix alba*, the white willow. Willow bark had been used for centuries by superstitious natives; could it be anything more than a silly folk-remedy? There were salicylic compounds in oil of wintergreen, too, and this plant remedy was a legendary cure for fevers and for rheumatism. What was all this?

Back to his scribbled notes, back to the fever records and the dizzy temperature charts. Back to the wards, where feverish patients, red-faced and perspiring, some of them almost hysterical, lay tossing on their beds. Back with more doses of salicylic acid and more temperature records to add to his notes. Now he hardly cared whether the patients lived or died—what he wanted was the

answer to that one burning question: *What does salicylic acid do to the temperature?*

After tests on scores of patients, he reported his findings in a scientific paper that was hailed from Copenhagen to Cape Town. "Salicylic acid," he announced, "has, in my hands, invariably reduced fevers. . . . The cause of the fever is not important."

Thus, by accident, medicine was given a fever-fighter—a drug that reduced high temperatures; a drug that, of greatest importance, was cheaper and more accessible than quinine.

Young Dr. Buss's findings could not be questioned. In spite of the fact that he was an unknown and untried researcher, his facts spoke entirely too eloquently; furthermore, they were checked immediately by a thousand doctors on tens of thousands of patients. Von Heyden's salicylic acid factory in Dresden soon had trouble filling all the orders that poured in for this amazing new chemical.

It made little difference, now, that imposing Dr. Ewald in Berlin utterly exploded Kolbe's hope that salicylic acid would cure every disease. After using the drug on all his typhoid fever cases, Dr. Ewald had announced: "We all agree that the mortality this year has been certainly no less, and perhaps even greater, than in former epidemics."

"Why worry about that?" his colleagues responded. "Even if we can't cure a disease, at least now we can reduce dangerous temperatures."

But there was one physician who wouldn't accept that sweeping generality. Said Franz Stricker, a stiff, dictatorial army doctor who had been working in Berlin hospitals: "I have found something else. I have tried salicylic acid on some of my patients who had rheumatism and fever. True, the treatment stopped the fever, but it also did peculiar things to the rheumatism. After two days of treatment, the swollen joints went back to normal, the reddening disappeared, and the pain stopped. I have tried salicylic acid on all types of rheumatism, and I have noted always the same results. I even notice this same relief when my patients have the rheumatic pains with no fever at all.

"Undoubtedly, salicylic acid is a specific against rheumatism!"

Once again the doctors were off on the trail, and again they confirmed another remarkable property inherent in salicylic acid. This drug not only brought quick relief to painful arthritic, rheumatic joints, but it also stopped other kinds of pain—neuralgia, sciatica, neuritis, and even headaches.

Salicylic acid might not be so good at killing germs, but it was certainly unsurpassed as a fever-fighter, rheumatism-cure, and painkiller!

(Back in Leipzig, old Hermann Kolbe muttered sadly, "And I thought I had found a germ-killer. Could I have made an error?")

II

This dazzling conquest over fever, rheumatism, and pain did not end there. The rapid sequence of salicylic acid discoveries (the whole affair had taken only three years) made scientists start looking for other and perhaps better fever-fighters and painkillers.

Salicylic acid seemed to be almost as cooling against fever as quinine and infinitely less expensive. It was not so potent against pain as morphine but a lot better and safer to control milder pains. It appeared to be unexcelled as an agent against rheumatism. Possibly, the scientists thought, we can get something still more wonderful.

They turned to quinine, the queen mother of all fever-killers. By now the German chemists were beginning to unravel some of its mysteries and to wonder what part of the quinine molecule was responsible for quenching fever. They devised a few quinine derivatives but dropped them quickly—all of them caused chills and collapse and turned the skin blue, and all of them wrecked the kidneys.

Then, just as Hermann Kolbe had introduced salicylic acid on the basis of a wrong theory, another German chemist was ready to make another brilliant mistake.

In 1883, twenty-four-year-old Ludwig Knorr at the University of Würzburg was hunting for the section of the quinine molecule that could reduce fever. Other scientists tried to discover it by taking quinine apart and studying the pieces. Young Knorr made up his mind to do just the opposite—to take simple chemicals, put them together, and then test the product.

It ought to be easy, he planned on paper, to synthesize something like quinine by mixing a little methyl-phenyl-hydrazine with some ethyl-aceto-acetate. The product of his actual experiment consisted of a batch of white crystals, tiny little platelets soluble in water and alcohol. Well, he thought, here it is, my synthetic fever-fighter. What am I going to do with it?

Then he remembered a man from his student days at the University of Erlangen, a Dr. Wilhelm Filehne, who knew a lot about fever and fever drugs.

"Dear Dr. Filehne," Knorr wrote, "I recall that some years ago you carried out the tests on various quininelike drugs. I have recently synthesized in my laboratory a new compound which is undoubtedly some kind of quinine derivative. Could you do me the great kindness to test this and give me the benefit of your experience and great knowledge?"

Fifty miles away at Erlangen, good Dr. Filehne smiled as he read this fateful request and kindly set about trying Knorr's chemical. He had tested so many before—they had all looked so promising at first—and now this one. Well, he thought, if I can spare a few hours next week . . .

Next week Dr. Filehne no longer smiled. This new chemical which the young Würzburg chemist had created was by no means just another drug. Filehne could hardly believe his own tests—the new drug was almost as good as quinine itself!

Knorr's crystals couldn't cure malarial fever, but on any other kind—pneumonia, tuberculosis, erysipelas, typhoid, typhus—they seemed miraculous. Every possible test in the laboratory and in the hospital showed that they were safe to use.

"My dear young friend," Filehne told Knorr, "I don't know what

your product is; I don't know its formula; but as an antifever drug, it is one of the most remarkable I have ever seen. If you have not already given it a name, may I suggest that, after the Greek word *pyretos* for fever, you call it *antipyrine.*"

The new antipyrine was not quite so marvelous as Filehne had anticipated. It was not so good as quinine, since it couldn't cure malaria, and it couldn't even cure every case of ordinary fever. But it was a remarkably effective drug and well deserved the glowing praises it won from the German doctors who tried it.

With the memory of the salicylic acid episode fresh in their minds, the doctors naturally tried antipyrine on rheumatism and on all kinds of aches and pains. They learned that it brought relief to aching, swollen joints and to patients suffering from headache, backache, and neuralgia.

Only after all these splendid reports had accumulated did Knorr suddenly discover that he had made a most embarrassing error. He had set out to make a synthetic quinine derivative which would fight fevers. (That was his only justification for daring to send his product to the famous Dr. Filehne.) Now he learned that his product was undoubtedly effective against fevers and against a great many other things, but it wasn't any quinine derivative—it wasn't any more like quinine than it was like sawdust. Antipyrine was a brand-new compound of a type that had never been seen in the world before.

Careful chemical tests showed that his proposed reaction between methyl-phenyl-hydrazine and ethyl-aceto-acetate didn't work at all as he had predicted. He had actually created a totally artificial drug that could be found nowhere outside of the laboratory.

Antipyrine was the first great completely synthetic drug. Its discovery marked the creation of a tremendous new business—the great synthetic drug industry. Germany quickly assumed command of this promising infant and nurtured it well. It soon became evident that the raw materials used by Germany's dye industry were also excellent raw materials for synthetic drugs, and that dye

factories could easily be modified and turned into drug factories.

Knorr turned over the patent rights and the manufacturing of his antipyrine to the huge Hoechst Dye Works near Frankfort on the Main. Here were trained chemists to work out all the details of large-scale production; here were businessmen to take over all the burdensome troubles of financing; here were "connections." And here, though no one suspected it then, was the beginning of Germany's forty-year monopoly of the world's synthetic drugs.

III

The first great fever-killers and painkillers, salicylic acid and antipyrine, were thus discovered by accident. It would have been fantastic to predict that such a thing could happen again. . . .

In 1886, the medical world looked to one small clinic at Strasbourg in German Alsace for a stream of new information on the stomach and the digestive tract. There, under the capable direction of Dr. Adolf Kussmaul, a host of young students tested the effects of chemicals on digestion. Working with terrifying stomach pumps, they learned how to flush out the stomachs of protesting but helpless patients. They sought cures for all the intestinal diseases caused by germs and parasites.

One day a pair of these young assistants was assigned to a new job. "Gentlemen," Professor Kussmaul ordered, "I have a nice tricky problem for you. Here's a nasty worm that gets into the intestines and burrows into the intestinal wall. Perhaps you can find some drug, some chemical which can kill it and which won't harm the patient."

This unexciting assignment went to Arnold Cahn, who had been working on the acids of the stomach, and to Paul Hepp, who had been hunting a cure for trichinosis. Neither was pleased with the new orders.

"Worms, worms, worms!" fumed Cahn. "I don't want to work with worms. Why don't you do it, Paul? You're the worm expert around here."

"I know," said Hepp, "you don't want to, and I don't want to, but the Old Man says we do it. Well, let's get started and finish it up in a hurry. What'll we try?"

"Umm, we might try some of the naphthalene if there's any left. Everybody's been using it around here." He turned around. "Ho, Julius! Come here!"

The sleepy, stupid-looking glass-washer-and-errand-boy ambled up to them. "Yes, gentlemen?"

"Go down to the drug room," Cahn ordered, "and tell Schmidtzie we want some naphthalene, about fifty grams, if he has that much left."

Julius wandered sleepily to the storeroom where Herr Schmidt lorded it over rows upon rows of compounds. The order was repeated, and an hour later Schmidt, himself, came up to make the delivery.

"Herr Doctor," he explained to Cahn, "I do not have enough naphthalene in the big stock bottle. But here, I've brought you an unopened bottle. There's plenty in it, though I'm not sure what it is. You see, the label has been damaged, and I can't be positive. I think it's naphthalene."

Cahn peered at the worn label and, still upset by the Old Man's assignment, jumped to a conclusion. "Yes, yes, of course it's naphthalene. Leave it here, will you, Schmidtzie; we'll probably use the whole damn bottle!"

A week later, Drs. Cahn and Hepp were still trying to kill worms with the new bottle of "naphthalene." They were more provoked than ever before—the chemical didn't work right (it didn't even smell right, had they stopped to think of it, for naphthalene should smell like moth balls!), and it didn't kill worms.

Finally Paul Hepp grabbed the bottle. "Give me that," he said. "I'm going to see if this stuff can cure anything! I've got a patient over in the clinic—his bowels are crammed with every infection in the textbooks. Let's see what this naphthalene does to his bugs!"

Three hours later, Hepp rushed up to Cahn's desk. "Hey! Listen to me! Did you know that naphthalene reduces fever?"

"The devil it does!" exclaimed Cahn. "Somebody or other in Berlin tried it, and it didn't work."

"So? Well, either somebody-or-other is crazy, or I am. And I think I'm sane."

"What do you mean?"

"Just exactly this. You know my ward patient? Well, this morning his temperature was five degrees above normal. I gave him a dose of this naphthalene," he shook the bottle, "and thirty minutes later, his temperature had gone down, boom, to normal. Now who's crazy?"

"Let's see that stuff."

Cahn examined the bottle of white powder. It was the same one Schmidtzie had brought up, the one with the defaced label. "You know," he began, "this just might not be naphthalene. . . . Here, smell it. See—no odor. Good God, Paul, this can't be naphthalene!"

Hepp whistled softly. "And we don't know what it is. Whew! I might have killed that fellow this morning! Look here, I've got a cousin over at the Biebrich dye factory. How about letting him analyze this for us?"

A few weeks, a few animals, and twenty-four patients later, the two Strasbourg physicians sent a brief article to the editors of a Berlin medical journal. "Through a fortunate accident," they began, "a new compound has come to hand, in which we have discovered an excellent antifever effect. This has been investigated by Herr Dr. E. Hepp in Biebrich and determined to be a substance long known to chemists. It is acetanilide. . . . We wish, however, to cover it with the descriptive name—*antifebrin.*"

Hardly six months after the announcement of antifebrin, another fever-fighter appeared. There was no mistake this time but careful medical and—strangely enough—economic planning.

It all began one morning when Carl Duisberg went to work on a vexing problem of storage. Down in the courtyard of the Friedrich Bayer and Company dye factory, where Duisberg was director of research, stood a great pile of yellowish powder which had

been accumulating until, by now, there were more than fifty tons of it.

"We've got to do something with that," Duisberg told his assistant. "It's taking up entirely too much space."

"What is it?"

"Crude para-amino-phenol. One of those useless by-products every dye factory has to worry about. Got any ideas?"

The assistant shook his head.

"Well, I have. Come over to my desk. Now, here's the formula of para-amino-phenol. All right, now over here is the formula of antifebrin, the drug those Strasbourg men brought out. See how much alike they are? Very well. I have a belief that if we acetylate this amine group here and then block out this phenol with a methyl or possibly an ethyl group, we might get something really practical."

Like magicians planning a new way to bring a rabbit out of a hat, these two chemists just as calmly sketched the transformation of a dye waste product into a potent antifever drug.

The whole job was exceedingly simple. Duisberg's suggestions were carried out on a small scale and yielded a product that at first was labeled ethoxy-acetanilide (even its name showed its relationship to Cahn and Hepp's acetanilide or antifebrin). Then the new product was rushed to the big hospital at Freiburg to be tested on patients.

When the tests were completed, that big pile of waste material in the factory courtyard was carefully collected and made ready for its large-scale transformation into a new drug, which from now on would be called *phenacetin*. It was found to be exceptionally safe, effective, and inexpensive, an excellent fever-fighter.

When they told Carl Duisberg about it and praised him for his uncanny planning, the chunky little chemist waved away the applause. "No," he said, "it was very simple. We cannot have great piles of waste in the courtyard. We must have a teamster haul it away or change it into something we can sell. . . ."

That expression, "Change it into something we can sell," became

the underlying philosophy of all German industrial chemistry. It carried Carl Duisberg to the very top of that industry, to the head of the I. G. Farbenindustrie, the great German dye and drug trust which he helped to create.

So here Germany had given the world four great drugs to battle fever and pain—salicylic acid, antipyrine, antifebrin, and phenacetin. Soon they turned out two more, *pyramidon* or *aminopyrine,* which is merely antipyrine with a few trimmings, and gout-fighting *cinchophen.* Every one of these six is manufactured by the ton, even today, for fever and pain are still the most common of all disease symptoms. But the Germans found a seventh drug that was still better.

In 1853 when Hermann Kolbe had first created salicylic acid out of carbolic acid, another German chemist prepared a derivative of this new acid, described it, and then promptly forgot about it, for it appeared to be totally worthless. It was acetyl-salicylic acid.

Not until 1899 was a moment's thought wasted on this acetyl-salicylic acid. It was just another chemical listed in the textbooks as a useless derivative of its influential relative; it wasn't even complex or mysterious. Everybody ignored it—everybody but clever staff chemist Felix Hoffmann of the Bayer Company. Chemist Hoffman had two good reasons for his interest. First, there were his orders from the Bayer officials: Get a substitute for salicylic acid, something that will be better than any fever-fighter on the market! And second, there was his father.

"Felix," cried Papa Hoffmann every night, "my rheumatism is bad again!"

"Yes, sure, sure. That's too bad. Did you take your pills?"

"Pills!" Poor Papa would bleat piteously. "Don't talk pills to me. They make me sick. They make my stomach feel like—like ants crawling in it! My throat burns! Those vile pills make me vomit every time. I won't take them. Rather have my rheumatism!"

"Yes, Papa, I know. I'm sorry you don't feel very well tonight. But you'd better take your pills. They're all right for you, good old salicylic acid."

"Ach, you and your salicylic acid! Felix, I send you to college to be a smart boy. Why don't you help me? In that nice shiny laboratory, why don't you find something for me?"

"Yes, Papa, I know," Felix would mutter absent-mindedly. "Some day I'll find something for you. . . ."

Every night the chemist went through that ceremony with his suffering father, and every day in the "nice shiny laboratory" at the Elberfeld works, he would toil slowly, patiently, painstakingly, tracking down a new fever-killer. It was inherent in the thoroughness of German research that eventually Felix Hoffmann would come across acetyl-salicylic acid. Those German scientists were so exquisitely thorough!

One day Felix carried a package of bitter, white, silky crystals to the pharmacology laboratory to Dr. Heinrich Dreser, head of Bayer's drug research department—the man who had introduced heroin as a safe substitute for morphine.

"Dr. Dreser," said young Hoffmann, "this is some pure acetyl-salicylic acid. We've finished with it in our department, and we think you might want to try it up here, perhaps on a few animals."

"Acetyl-salicylic acid?" Dreser fingered the powder. "Think it might be a substitute for salicylic acid?"

"Well, doctor, you people will have to decide that, you know. We've just done the chemistry on it."

"Naturally. Thank you for bringing it up. I'll confer with you in a week or two."

Dreser's work took much longer than a few weeks, but when it was finished, there was a good deal to tell. "You've really got a surprising compound here," he told Hoffmann. "We've given it some tests, some very rigorous tests. . . ."

"And?"

"And it's beautiful!" Dreser smacked his lips emphatically. "You can be proud of your share in this work."

Hoffmann bowed politely. "Thank you, doctor, but there's one thing I want particularly to know. Is the new chemical very irritat-

ing? You understand, perhaps, that I am personally interested in that side of it."

"Yes, of course, your poor father. Well, come over here, and I'll show you something!"

Hoffmann followed Dreser to a little aquarium in the corner and watched the pharmacologist splash and curse until he had netted two small, wriggling minnows. Each was quickly wrapped in a wet linen bandage, a rubber tube placed in its mouth to provide artificial respiration, and a siphon hooked up to sprinkle water over its gills.

"How do you like this arrangement?" asked Dreser proudly. "Now, watch. Look at these little devils, at their tail fins especially. See how clear and transparent the membranes are? All right, now I dip fish A's tail into a dish of salicylic acid solution, so. And fish B's tail goes into this other dish containing acetyl-salicylic solution, there!"

Amazed at this bizarre experiment, Hoffmann stood speechless.

Dreser smiled at him. "Don't you understand? But just look—see this fish, the one in the salicylic acid—its fin is already beginning to turn white and opaque. That's a sign of irritation; that shows what salicylic acid does to your guts.

"But now look at this other little fellow. See? His tail is as good as new. No whiteness, no opacity. See how clear it remains in your acid?"

Light dawned on Hoffmann. "You mean you can use this test to prove my acetyl-salicylic acid is harmless?"

"Certainly, my boy, certainly."

"Whew!" whispered the chemist, "that's wonderful. But don't you have to try it on other animals and on human beings?"

Dreser nodded vigorously. "That must be done, and it has been done! I've sent samples to Witthauer at the Deaconess Hospital in Halle and to Wohlgemuth in Berlin. They have already told me the trials were entirely successful!"

Not until many months later, until actually millions of patients had tried this new drug, did scientists realize that it wasn't entirely

safe. Not until then did they become aware of the occasional additional effects of the drug—peculiar headaches, nausea and vomiting, temporary deafness or ringing in the ears, constriction of the throat, strange swelling, and bothersome rashes. Now the two men were full of the thrill of victory.

"There's actually only one thing I don't like about this drug," Dreser remarked in his glowing optimism. "It's name is all wrong. Acetyl-salicylic acid. Too long and too infernally complicated!"

"Well," suggested Hoffmann, "let's abbreviate the 'acetyl' and just use the first initial. Then we could call it 'a-salicylic' or 'a-salicin.' "

"No good," said Dreser, "we should get away from the word salicylic entirely. Its reputation is too unpleasant."

"Well, then, here's an idea. You know, perhaps, that about sixty years ago someone found salicylic acid in *spiraea* plants. He didn't know it was salicylic acid, thought it was a brand-new chemical, so he called it spiric acid. How about calling our drug acetyl-spiric acid or . . . or just simply *aspirin?*"

Dreser thought for a moment. "That's not bad," he admitted. "Acetyl-spirin. A-spirin. Aspirin. Um-hmm, that's all right—nobody will know what it means, but it will be so easy to pronounce!"

CHAPTER VII

Synthetic Lullaby

FISCHER, VON MERING, AND THE BARBITALS

JUSTUS VON LIEBIG's first explosion was relatively mild. It could hardly be considered a real explosion at all, just a slight accident that spattered a kettle of paint all over his father's workshop in the German city of Darmstadt.

"Justus," Papa von Liebig reproached, "I have asked you not to play with the paints. Why can't you stay at home and study your books or something?"

Eleven-year-old Justus wiped a blob of paint from his hair. "Papa, I don't want to study my books. I want to work here with you. I want to mix paint and help you."

But Papa felt, all things considered, his paint business would do better without such help, and Justus was packed off to school, to the Gymnasium, where he could learn languages and mathematics and grow up to be a real businessman.

The second explosion was infinitely better. It happened one afternoon in 1819 and abruptly terminated Justus' stay at the Gymnasium.

"I do not know what to do with you," declared the Rector. "Observe what you have done with your nasty chemicals. Look, the entire wall is cracked, and the window is now in the street. For months you have been the plague of your teachers. You must, indeed, be a terrible sorrow to your parents. What do you think will become of you?"

"I," announced Justus, "am going to be a chemist!"

So Justus was sent back home; but he didn't stay very long, for

his father still had other ideas. "Chemist? Nonsense, my boy, we'll make you a pharmacist. I'm going to send you to Heppenheim where I've arranged for your apprenticeship."

The third explosion came ten months later, and this time young von Liebig made himself a wonderful one. It went off with a soft, velvety *oosh* that lifted the roof off the pharmacy attic, blew out windows, knocked doors from their hinges, and catapulted the startled apprentice clear across the house.

Again Junior and Senior von Liebig faced one another. "Justus," demanded Senior, "what is to become of you? Why, why couldn't you be a good apprentice?"

"But Papa, I don't want to be a pharmacist. I want to be a chemist."

So in 1820, seventeen-year-old Justus entered the University of Bonn to study the sciences, and the explosions—or at least the people who scolded Justus for them—came to an end. He worked at Bonn just long enough to discover that he couldn't learn any chemistry in Germany. "In 1820," he wrote later, "the best German laboratory wasn't even a good kitchen." He decided to move to Paris, to join the group that clustered at the feet of the French master, Gay-Lussac.

In Paris, a veritable giant of a man came up to him one day and began asking questions. "What are you working on?" he inquired.

"On fulminate of silver, sir," replied Justus.

"Are you now? Well, what have you discovered?"

Justus told him, politely, but in enthusiastic detail. The big stranger seemed impressed. "Ah, you have made some findings. I wonder if you would like to have dinner with me on Sunday. We can talk about this a little more."

Sunday came, and Justus, dressed in his best suit, was bubbling with excitement when a terrible thought struck him. Who was the man? What was his name? Where did he live? Justus had forgotten to ask. . . .

On Monday morning, when he entered the laboratory, one of the students rushed up to him. "Von Liebig, where were you yester-

day? Why didn't you come to dinner? They waited and waited for you!"

"I know. I'm terribly embarrassed. But I forgot to ask the man's name."

"You forgot? You *forgot?* Didn't you know you were invited by Baron von Humboldt, the greatest scientist in the world?"

Von Liebig snatched off his apron, rushed to the scientist's home, and profusely sputtered what von Humboldt finally understood to be an apology and an explanation. The great man, roaring with laughter, fell back into his chair. Then, wiping the tears from his wrinkled face, he fully forgave the quaking young chemist and proffered another invitation for the next Sunday.

Von Liebig couldn't have made a more influential friend, for in 1820 Friedrich Heinrich Alexander, Baron von Humboldt, was without peer among scientists. A naturalist and geographer, he had explored the Amazon and the Orinoco, climbed the Andes, and visited Mexico; he had introduced exotic new South American products into Europe; he had performed brilliant investigations on temperature, natural history, magnetism, volcanoes, and rocks. And, when Justus von Liebig was ready to leave Paris, von Humboldt wrote letters to the proper people and obtained for his young friend the post of professor of chemistry at the old German university at Giessen.

Professor of chemistry? The old-timers shook their heads. What were things coming to? Chemistry! How could the authorities flatter that disgusting business of smells and slop by assigning a professor to teach it?

Von Liebig didn't know how to teach it, either. He was only twenty-one, and there were precious few professors of chemistry in all of Europe. But he began boldly, and soon the other teachers were watching him. In a few years, this genius was well on the way to making his little university the most exciting place in the world for men who wanted to become chemists. Students came to him from every country to listen to his lectures and to watch this master perform his experiments.

In 1831, one of these experiments opened a new field for medicine (although medicine didn't realize it then); von Liebig bubbled chlorine gas into alcohol and obtained a new liquid which he named *chloral.* Then, by treating chloral with very strong alkali, he obtained another liquid which he called *chloroform.*

II

On the other hand, Oscar Liebreich wanted to be a sailor. Oscar Liebreich, who eventually picked up where von Liebig left off, had not the slightest inclination to be a chemist, a doctor, or any other kind of scientist.

The chloral-chloroform discovery was seven years old when Liebreich was born in Koenigsberg in East Prussia. Before he celebrated his tenth birthday, chloroform had been introduced as a marvelous anesthetic for painless surgery. Medicine underwent one of its great revolutions, surgery became a real boon to mankind, and chemistry and the other sciences mushroomed into every field of human activity. But Liebreich still wanted to be a sailor.

It took only one voyage to transform cabin boy Liebreich into student Liebreich. He decided he was not meant for the sea and turned to the study of chemistry and then to medicine.

In 1868, four years out of medical school, he was working in Berlin and seeking to apply chemistry and chemicals to the cure of diseases. In particular, he sought a cure for insomnia.

In those days, there weren't half a dozen sleeping potions which were effective, there weren't three which were safe, and there wasn't one which was both—both safe and sure. Bromides were too weak, and morphine, ether, chloroform, marihuana, hashish, and a host of others were much too deadly to use night after night without the constant vigil of a doctor.

"About the best," Liebreich admitted to himself, "is a hit on the head with a hammer." It was probably as effective as anything else.

But there should be something else—there *must* be something else. There must be some drug that could be taken easily, that

would sing a chemical lullaby to sleepless patients, and that, above all, would be safe to administer. Liebreich, the physician, became Liebreich, the chemist, on the track of a sleeping potion.

There were possibilities in that report—now nearly forty years old—by Justus von Liebig: Mix alcohol and chlorine to make chloral; treat chloral with alkali to make chloroform. "Hold on," thought Liebreich, "I can use that. Chloral plus alkali gives chloroform, and chloroform puts you to sleep. What would happen if I put some chloral into the blood stream and let the alkali in the blood go to work on it? It's an idea!"

So Oscar Liebreich determined to turn blood vessels into test tubes. There was alkali in the blood, although only a very little bit, and it ought to work on chloral, to turn it into sleep-producing chloroform. It ought to work just as it would in a glass test tube but more slowly. It ought, he dreamed, to produce chloroform slowly over many, many hours—it ought to put his patients to sleep and keep them that way for as long as he wanted!

If he had done the logical, the scientific thing first, the whole idea would have blown up. If he had mixed a little blood with a little chloral in a test tube to see if any chloroform had been created, he would have given up his dream as hopeless. For no matter what his theory indicated, chloral and blood will not turn into chloroform. But Liebreich didn't know that.

Instead of doing the sensible thing first, instead of a test-tube experiment, he started at once on animals—on big squirming frogs. Under their skins he injected a fraction of a drop of chloral. The frogs promptly went to sleep.

"Ah-ha!" he chortled. "I knew it! Those big fellows are practically snoring. My chloral turned into chloroform . . . wonderful!"

When the frogs woke up and hopped around again, active and well, Liebreich tried the same test on rabbits and on dogs. They, too, collapsed in a few minutes, went soundly to sleep, and awoke hours later full of life.

Liebreich trotted off to the wards, a flask of chloral in his hand. At the Charité Hospital, he was given permission to try his magic sleeping potion. First, of course, on insane patients; for even if they should die, it wouldn't be too great a loss.

In one bed lay crazy Herr Stoekel, who had been diagnosed as an epileptic, suffering also from delusions and profound anxiety. Afraid that his bed would catch on fire, he remained awake day and night. The doctors wanted Herr Stoekel to get some sleep, so into his arm Oscar Liebreich shot twenty drops of chloral mixed with a little water.

In three minutes, the patient began to yawn and blink his eyes. "I don't want to sleep," he muttered, "go away, please go away. . . ."

In ten minutes, his eyes were closed. He tried to open them, but it was too much trouble.

Within an hour, Herr Stoekel was sound asleep. Pinpricks could hardly rouse him. He slept for three hours, when he awoke for lunch, and then went back to sleep again.

Three times epileptic Herr Stoekel took his shots of chloral, and three times he sank into the sleep he feared and needed so much. Then Liebreich gave chloral injections to a middle-aged woman, her mind wrecked from progressive paralysis, and to a beautiful young girl cursed with hideous illusions.

They all went to sleep, and they all awoke refreshed. Then the doctors, high with enthusiasm, tried it on other patients—patients who couldn't sleep because of pain, patients who couldn't sleep because of worry, patients who just couldn't sleep. And chloral put them all to sleep, night after night, while they regained their strength and health.

Liebreich was so happy with his results, so delighted his theory had turned out right. Months later, when they proved his theory was all wrong, that chloral did not turn into chloroform, that it actually did the job itself, he still felt pretty good. And even when another German doctor proved he had used chloral eight years

before but had forgotten to announce it, Liebreich refused to be upset. After all, it was he, Oscar Liebreich, who had given the world a safe sleeping potion.

III

But chloral was actually no safe drug to be turned loose on the world. It had addicting properties, like cocaine and morphine, that turned occasional users into haggard men and women who couldn't live without it. It had dangerous after-effects—sometimes patients took chloral safely for one night, for two nights, for as long as a week, but tried it once more and didn't wake up. It had entirely too much value for captains who needed to shanghai a sailor and for personnel managers of illegal resorts; to them chloral became famous as "knockout drops." It became the ideal weapon for suicides and murders.

Doctors, nevertheless, kept on using chloral. "With all the tension and the rapid pace of modern life," they said, "chloral can provide the necessary relaxation." This was the rapid pace of the 1880's.

And then there were sick men and women who might die if they didn't sleep. Chloral, though dangerous and addicting, was the best the doctors could give them; but they prayed for something better and safer.

Oscar Liebreich had announced the discovery of chloral in 1869. In that same year, seventeen-year-old Emil Fischer went to work for his father in a German lumber mill. Just as chloral-discoverer von Liebig started to be a businessman, just as chloral-user Liebreich started to be a sailor, so Emil Fischer started to be a lumber merchant. And young Fischer wanted to be a chemist.

It took two years before Emil's father came to the bitter, disappointing conclusion that his son was not made for business. "Ach, you're too stupid to be a merchant," he admitted. "You might as well go to the university. Already you're a failure!"

So Emil Fischer, who was destined to become one of the greatest chemists the world has ever known, went to school at the University of Bonn, where Justus von Liebig had started, and then to the University of Strasbourg. Strasbourg, then a German city after the Franco-Prussian War, was gay and glittering and colorful. The departing French had left the cancan in the cafés, and the arriving Germans had brought swarms of roistering, beer-drinking, duel-loving students. And professors!

What professors came to Strasbourg in those days! Men like the immortal Adolf von Baeyer, with his comical, bearded, billiard-ball head, and Hoppe-Seyler, who was playing midwife to the new science of biochemistry, and von Krafft-Ebing, who was trying to make sense out of sex, and Oswald Schmiedeberg, greatest teacher of the drug-hunters. This was the German university city at its best, and it intoxicated young Fischer. He worshiped his professors all day and celebrated with his fellow students all night. He swore eternal friendship with bright young men who had come from all over the world, with merry Josef von Mering, who could handle a saber better than a test tube, and with the flock of Fischer cousins who always turned up.

Of all the professors, Fischer admired von Baeyer by far the most, and when that great scientist moved to Berlin, Fischer trailed along. When von Baeyer moved to Munich, Fischer went with him.

Meanwhile, Emil Fischer had been doing more than bowing at the throne of the mighty: he had been making discoveries of his own, brilliant discoveries of a sugar-testing chemical known as phenyl-hydrazine (and an insidiously deadly chemical it was), discoveries of dye formulas, and new ways to create the caffeine of coffee and the theobromine of chocolate.

When he was thirty, Fischer became a professor himself and left von Baeyer for the University of Erlangen. Soon there were more discoveries—an amazing way to make synthetic sugar and to study the structure of sugars with his phenyl-hydrazine.

"That young Fischer," they were saying, "is already famous. He's

one of the four or five best chemists in the world, but he should look out for that phenyl-hydrazine. It's bad stuff. He shouldn't keep inhaling the vapors."

Three years later, Fischer moved to the University of Würzburg, and now admiring students followed him. There was more research on sugars—compounds once thought to be beyond the range of chemistry—and new studies on chemicals secreted by the kidneys. With his fame and future assured, Fischer thought it was safe to marry, and he wed tall, beautiful, witty Agnes Gerlach, who soon gave him three handsome sons.

Finally, in 1892, the highest honor that Germany could bestow was offered to him. He was called to a full professorship at the greatest German university, Berlin.

The sugar investigations continued, but now Fischer started on the most difficult chemical problems which could then be imagined, the study of enzymes and proteins. Here were secrets that had been buried for a billion years in the cells of bacteria, in the mysterious action of digestive juices, in the components of meat and milk and eggs—the very secrets of life itself. No one had yet dared to till these two fields; certainly no one had made any mark upon them. But Fischer was convinced that even these complicated enzymes and proteins were chemicals, and he would not be bluffed by any mere chemical.

Just as he began this new work, word came that he had been awarded the Nobel prize in chemistry. He was now fifty years old. "Ah," he said, "if only my father were alive to see what has happened to his stupid son. . . ."

But suddenly Emil Fischer had become old, cranky, restless. He barked at his students without cause; he was grumpy and nervous. The phenyl-hydrazine vapor he had inhaled for years, the chemical he himself had discovered, was beginning to rot his body. And then Josef von Mering walked into the laboratory.

Von Mering had been born in the city of Cologne in 1849, three years before Fischer, and had studied medicine at Bonn, Greifswald, and finally at Strasbourg, where he and Fischer had become

fast friends. Soon after Fischer had gone off to Berlin with von Baeyer, von Mering took his brand-new M.D. degree and made the rounds at Berlin and Leipzig. But while universities and industrial laboratories came with splendid offers to Fischer, nobody came to von Mering.

Von Mering wanted to be a doctor and a good one, but his heart wasn't in it. If it hadn't been for the diploma neatly framed in his office, even his few patients would have been convinced he was treating them under false pretenses.

"How is it," one of them asked, "that he can't keep his mind on his business? He tells me to stick out my tongue and then asks me how sugar is digested in the stomach."

"I know exactly how you feel," said another. "I ask him what causes my headaches, and he lectures me on how nitro-something-or-other poisons a dog."

"And do you know what he did to my wife? The poor woman was sick at her stomach, and he describes to her how he injects food into the veins instead of the stomach. It made her even sicker!"

But how could von Mering stick to business? How could he worry about a patient's aches and pains, when he had such engrossing mysteries which kept his mind back in the laboratory? If he could have kept a patient's confidence with a little discreet hand-patting, he invariably lost it by lecturing him on the value of scientific research. It was a pity, since patients wanted to like Dr. von Mering; there were few men who had his bigness, his jollity, his constant flow of good spirits.

"Nevertheless," they said, "we want a doctor to cure our aches. We can get our laughs without paying so much for them. We'd better go to another doctor."

So poor von Mering—even he laughed at the joke of it!—couldn't make a decent living. The only job he could get and hold was the insignificant position of "bath physician" at the Salzschlirf spa, and that was merely a summer job.

His labors at the resort, however, marked a turning point in his career. He met Maria Fuxius there and married her, and Maria—

so feminine, so tender and wistful during the courtship—promptly went to work on her husband.

They went back to Strasbourg and von Mering was all seriousness. Pushed by his wife, he finally obtained an assistantship in the physiological institute. Now he could ignore patients and devote himself completely and delightedly to test tubes, rabbits, and dogs.

"Patients really bored me," he admitted. "What could they know about disease? But now . . ."

He started his investigations with a study on Oscar Liebreich's chloral and, trying to discover how it worked, slaughtered mounds of animals. "But how can I find out?" he asked. "Sleep is tied up with the chemistry of the brain, and nobody knows anything about that!"

He turned to the chemistry of the brain, ran into a maze of inexplicable results, and decided to take up the study of poisons. He found one poison, nitrobenzol, that killed dogs by producing diabetes in them. Then he found another, phloridzin, that did the same thing.

"Remarkable!" he cried. "Here are two chemicals that cause diabetes in dogs. But dogs practically never get diabetes. And then those two chemicals never get into human beings who do get diabetes. What is the significance of all this?"

He gave up this puzzle, after his minor contributions won him an assistant professorship, and went back to chloral.

"No use in trying chloral on dumb animals," he told Maria. "They can't tell you how it feels. We'll have to work on men."

The only patients he could get were prisoners in the Strasbourg jail, and so he relieved the boredom of murderers, thieves, and wife-beaters by putting them to sleep with chloral. Soon he developed a chloral derivative, amylene hydrate, and considered himself an expert on this business of synthetic sleep.

"In just a little while," he promised, "we'll have the whole answer to the mystery of sleeping."

But the solution wasn't that easy, and once again he pigeonholed

chloral and turned to diabetes. Again he found a trick that would produce diabetes—not a chemical, this time, but a simple operation. With surgeon Minkowski, he cut the pancreas out of a dog, and the dog immediately became diabetic and died.

This experiment was vastly more important than those little tests with nitrobenzol and phloridzin. If the two scientists had only been able to find what could possibly be in the pancreas that *prevented* diabetes. . . .

The gods of science were cruel to diabetics that day, for von Mering turned back to more experiments on chloral. The gods were kinder to those who begged for sleep.

A year later, von Mering was offered a real position, a full professorship at the University of Halle. Of course, Halle was a little university and couldn't compete at all with great Strasbourg, but a full professorship wasn't to be sneezed at. On Maria's advice he took it.

For nine years, the great medical centers heard practically nothing of Josef and Maria von Mering. Buried at Halle, he stayed at his work, wrote a moderately important textbook, and was adored by his students and his colleagues. "Old von Mering," they began to call him. "He's not a great scientist, but God bless him, he's always got a laugh for you, always a friendly word. And the stories he can tell!"

And then on a fateful day in 1903, von Mering realized he had run into a problem too big for him. He had an idea, an astounding idea, but he didn't know what to do with it; so he went to Berlin, to the great chemical laboratory on the Georgenstrasse, and there he met Emil Fischer again.

"How do you do, Professor Fischer," he began. "I don't know if you remember me, but I've come to . . ."

"Remember you?" boomed Fischer. "Josef von Mering! My dear old friend, where did you come from? How glad I am to see you. But where have you been? What have you been doing? Here, come into the office. Sit down, Josef, sit down. Why, I haven't seen you since . . . Ha! Now talk! Tell me everything!"

Josef von Mering sat there, speechless. For the first time in his life, this man who knew and loved everybody was embarrassed. His eyes were shining wet. "Emil, I—I wasn't sure. You're so famous now, a Nobel prize winner and everything, I didn't think you would see me. I thought—I was afraid you'd be too busy."

"Too busy? Too busy to see you? Ach, Josef, where do you get such fool ideas? Come, we shall close up the laboratory and go home to lunch. You must see my boys, three big fellows now, and then we shall talk about Strasbourg. Strasbourg, Josef, do you remember, eh? Remember those days, the beer and the singing and the parties. . . . Come quick, we must get out of here before somebody calls me."

For hours that afternoon, they talked and talked—of the old days at Strasbourg and the new days at Berlin, of the old professors, dead and gone, and old friends and old sweethearts. Von Mering soaked it in like warm sunshine. Reluctantly he brought up the reason for his visit.

"Emil," he said, "I know you must be dreadfully busy, but no one else can help me."

"Help you? Of course, Josef. You started to tell me this morning. You have some trouble at Halle? Perhaps you will let me offer a little loan? What can I do?"

"No, it's nothing like that. Let me put it this way." Von Mering hitched up his trousers and sat on the edge of his chair. "Do you know anything about hypnotics?"

"Eh, hypnotics? Some kind of pills, aren't they? To put you to sleep?"

"Exactly. I don't suppose you chemists worry about sleep, but it's very important to us doctors. You see, sometimes it's vitally necessary that we put a patient to sleep—to cure his insomnia or to give him rest that he needs, to quiet him before an operation, or even to calm some types of lunatics."

Fischer wagged his head. "I see. I didn't realize it was so important. This sleep that you want to produce—sometimes it really saves life, eh?"

"*Herr Gott,* yes! A good hypnotic would be as important as a good anesthetic or a cure for some infection!"

"Well, well, well!" Fischer declared. "This is all news to me. I must tell that to my students. They will be interested."

"Go ahead and tell them," von Mering agreed, "but be sure to tell them that a *good* hypnotic would be that valuable. And there isn't any such thing. That's why I've come to you, to get a good one."

Fischer protested. "But really, my friend, that is out of my field. I can't suggest anything that might . . ."

"You don't have to. Look here, give me a pencil and a piece of paper, and I'll show you."

Quickly von Mering listed the names of chemicals—potassium bromide, alcohol, chloral, morphine, hashish, sulphonal, and half a dozen more. "Here are the best sleep-producers we've got, and every single one of them has some bad property."

"Fine business," Fischer snorted. "A dozen good drugs and none of them good for much."

"Correct," agreed von Mering. "But I have the solution. I brought it with me."

"You've found it already? Wonderful. Let's see it."

Out of his pocket, von Mering fished a wrinkled, grimy paper and flattened it out before Fischer. "Here is the diagram," he told the great chemist. "Here is the formula for my chemical, for my little synthetic lullaby that can sing the world to sleep—and with safety, too!" He reached into another pocket and brought out a tube full of beautiful white crystals. "And here is the product!"

"Splendid!" exclaimed Fischer. "So that's the great discovery. But where do I come in?"

Von Mering hesitated. "Well, my—my great discovery, as you called it, doesn't work. Something slipped. The formula is right, but the product is wrong. All wrong. It doesn't produce sleep."

Fischer howled in laughter. "My dear old friend," he said. "I don't know whether you need a doctor or a chemist, but you certainly need something. Here you make the best sleeping powder

in the world, and it's so good that it keeps you awake! Come now, Josef, tell me—what happened?"

Von Mering picked up the piece of paper. "Well, here's the chemical I wanted to make—di-ethyl-barbituric acid. It contains these two sleep-producing parts, urea and two ethyl groups connected to the same carbon atom."

"So. And how did you make it?"

"By condensing urea and di-ethyl-malonic acid with phosphor-oxy-chloride."

"With that stuff? Josef, that's no way at all—you couldn't make your sleeping powder out of that mixture in a thousand years! No wonder your crystals won't work. They're something else. Here, let me borrow that formula for a couple of days. You don't need a doctor, Josef—you need a chemist!"

Fischer walked out of the room and went to the foot of the stairs. "Alfred!" he called. "Come down here!"

In a few minutes, a young man entered the room. "Josef," Fischer said, "this is my nephew Alfred—Alfred Dilthey. And Alfred, this is an old friend of mine from Strasbourg, Professor von Mering of Halle."

"How do you do, Alfred."

"Herr Professor."

"Alfred is living with us now," Fisher continued, "and is helping me at the laboratory; we're going to make a chemist out of him. Alfred, here is the formula of di-ethyl-barbituric acid. Professor von Mering thinks it might be very valuable as a sleeping medicine, and we're going to make it for him. . . ."

"But Uncle Emil, you said we had so much work to do that we would never . . ."

"Shush, Alfred!" Fischer turned to von Mering. "My nephew is new with us. He doesn't know that when I say 'never,' I mean 'not unless'. . . . Please, Alfred, no comments. We start tomorrow morning!"

Von Mering had put his problem into the most capable hands in Europe. If anybody could make di-ethyl-barbituric acid, that man

was Emil Fischer. But von Mering didn't guess that Fischer was struggling under an unbelievable load of work—his own researches, problems of organization, obligations to students and visiting dignitaries. Von Mering merely watched in amazement as Fischer guided his nephew Dilthey's creation of the new sleep-producer. At length, Dilthey and his uncle prepared not only di-ethyl-barbituric acid but eighteen similar compounds as well.

"Here they are," said Fischer. "But what in Heaven's name can you do with them? They all look the same and taste the same and feel the same. How do you tell which is a good medicine?"

"That is my job," said von Mering. "What the problem needs now is a good doctor. Here is where I go to work!"

He went to work with a vengeance, trying every one of the new chemicals on dogs. Some of the products, he found, had no effect. Others were so dangerous that they produced a sleep from which his dogs never woke. But there were others that had real possibilities—one that produced forty-eight hours of safe sleep, another that lasted for twenty-four hours, another that produced eight hours of sleep followed by six hours of grogginess. But the best of the lot, he decided, was actually di-ethyl-barbituric acid, the very compound he had sought for so long. In dogs it produced eight hours of deep sleep from which the animals woke rested and frisky.

In March, 1903, the results were announced in a brief report signed by von Mering and Fischer. They described the tests on dogs, together with a few experiments on human beings.

Already they had decided that no compound could be put on the market with such a title as di-ethyl-barbituric acid. Instead, they named it *veronal*, after the Italian city of Verona, which von Mering thought the most restful place in the world. Veronal was the first of a great new class of sleep-producers, the *barbitals*.

Within a few years, other workers delved further into the barbital clan and brought out even better and safer hypnotics, drugs like *luminal* or *phenobarbital* (which von Mering had overlooked in his first tests) and *nembutal, seconal, pentothal,* and dozens of

others. These barbitals gave medicine a tool of utmost importance; they gave physicians the control of sleep.

With but two exceptions—*paraldehyde,* used in the early stages of childbirth, and *avertin,* a combination of paraldehyde and bromine—these splended barbitals had no competition. They drove chloral, their honored predecessor, from the field.

If Fischer and von Mering had been superstitious, they might have worried for a moment about the fate of Oscar Liebreich, who gave the world its first great sleep-producer, chloral. They might have shaken in their boots to think that Liebreich died in such intense pain he had to use his own drug to steal a few last seconds of peace.

But Fischer and von Mering were scientists. They weren't at all superstitious.

Five years after the discovery of veronal, von Mering went to Italy for a much-needed rest and came back with a miserable attack of pneumonia. For weeks he lay in bed, suffering from terrible pangs in his chest and from the intense agony of the gout which had cursed his last years. For weeks he lay there, sweating in agony, until he was released by death. Veronal eased his last days.

That left Emil Fischer, but Fischer certainly wasn't superstitious.

Year after year, this great man kept at his work. The death of von Mering robbed him of the pleasure of renewed friendship, but he had work to do, more work on his enzymes and proteins. Now it was becoming much, much harder to keep at it. The deadly fumes of phenyl-hydrazine, the chemical he had used so many years before, had done their fiendish work well. It was harder, too, to sleep at night, to keep from snapping at his friends. . . .

Emil Fischer was sixty-two when the first World War broke out. The war robbed him of his nephew and coworker Dilthey, who was killed by the Cossacks in Poland. It took his son Alfred, an army doctor killed by typhus fever in Rumania. It twisted the mind of

his son Walter, who killed himself. It took away his friends from England, France, and America, and it took away his science.

At the end, Germany's defeat shattered his last dream—the invincibility of his country.

Emil Fischer died in 1919. Veronal softened the last agonies of the poisons which had devastated his body and his mind. It ushered in his final sleep.

CHAPTER VIII

Food Against Death

EIJKMAN AND THE VITAMINS

THIS is the story of the vitamins and Christiaan Eijkman, of the Americans, Elmer McCollum and Conrad Elvejhem. It is the history of the men who borrowed dreamy superstitions from little brown natives and wise old seamen, who found a strange "thing" in foods, and who magically transformed this "thing" into bright new weapons against death.

Eijkman, McCollum, and Elvejhem weren't the first of these vitamin-hunters. Ten thousand years before them, there must have been men who found a cure for the hungers that lasted even when bellies were full. And these three possibly weren't the greatest hunters, either; if they had never lived—or if they had pitted their skill against a ditch to be dug or neckties to be sold—even then, others would have come along.

But these three did live, and they did help track down the foods that halt death, and in so living and working they restored millions to health.

Far up on the northern point of the island of Sumatra, where the Dutch East Indies come to an end across from the Malay Peninsula, is Kota Radja, age-old capital of the Achinese.

These Achinese were a fierce warlike people who much preferred dying in battle to living in peace, but who wisely stayed close to the protective arm of England. Eventually, England withdrew that protection, and a Dutch army marched against Kota Radja. For a quarter of a century, the Dutch won battle after battle, cam-

paign after campaign, and steadily lost the war. These thin, mournful little Achinese had too many allies—steep mountains ideal for guerrilla bands and ambushes; rushing rivers as good as trenches; and particularly an insidious death that cut each Dutch army to shreds—a death not of bullets but of hunger.

This death, which bothered the Achinese not at all, was beriberi.

Beriberi? The Dutch army doctors knew beriberi, as for that matter, who didn't? This old, old sickness had killed in biblical days and in ancient Greece and Rome. It had paralyzed and rotted muscles in Egypt, turned men into living skeletons in Japan, wrecked hearts in China, made thousands of swollen, useless cripples in the long European wars. And it killed without respect to class—rich men, poor men, soldiers, sailors, statesmen, and criminals. Now beriberi broke out again to scourge the helpless army of the Dutch.

Hospitals were built down in Java and Celebes and the other lovely islands and were swamped in a fortnight. Beds were provided for a few hundred, and thousands were brought to lie in them. This was no sudden, sharp outbreak that came like lightning and vanished as fast. It went on and on, year after year, and the little Achinese defenders laughed to see the Dutch die without benefit of bullets.

After ten years of this carnage, the Dutch in Java wrote to their learned colleagues in Holland, to the universities at Leyden, Utrecht, and Amsterdam, and begged for help. "Find us a cure for this disease," they entreated, "or we are ruined!"

In Europe, the wise scientists clucked over this request. "Disease?" they murmured. "It must be caused by a microbe. Let us send our best microbe-hunters down to the Indies and let them find this elusive killer." So they selected Cornelis Pekelharing, professor at the University of Utrecht; he was a good man—he had studied proteins in the state veterinary school, and at Utrecht he had found the bug which he thought makes men bald.

They also selected Professor Winkler, who had once written a

thesis on the tubercle bacillus (which he couldn't find) and who really knew a lot about nervous diseases.

Then these two traveled to Berlin to get aid from the great Robert Koch, the master microbe-hunter who had just found the tubercle bacillus.

"I should like very much to go with you, myself," said Dr. Koch, who always wanted to go to exotic countries, "but I cannot now leave Berlin. I call your attention, however, to a young student of mine—and a countryman of yours—Dr. Christiaan Eijkman."

Young Dr. Eijkman, only twenty-eight when Koch recommended him, already knew beriberi. Two years before, he had served as military surgeon in the little Javanese town of Tjilatjap and had seen for himself what beriberi did.

So Pekelharing and Winkler, with Eijkman and several other sober young Dutchmen to do the drab, unimportant detail work, left Holland in October of 1886. In November they arrived at Batavia and started work in the tiny laboratory assigned them in the Weltevreden military hospital. They spent three months in the laboratory, three months working in the field, and three months in the laboratory again. Exactly nine months after they came to the Indies, the commission sailed back to Europe.

They had not found "the microbe that causes beriberi."

Of course, they reasoned, there must be such a microbe. Wasn't beriberi a mysterious disease, and wasn't every mysterious disease produced by a microbe? But all they could dig out was a puny little germ—present in only fifteen out of eighty human beriberi victims—which, when injected into a dog, made the animal very sick and sometimes wrecked its nerves.

Therefore as they sailed for home, concluding that this tiny, weak, unimportant little bug "was probably the cause of beriberi," they admonished the Javanese doctors to use vast quantities of corrosive sublimate and other potent germ-killers on clothes, floors, furniture, walls, ceiling, and all other exposed surfaces. (It was a great waste of corrosive sublimate!) But they did have one brilliant inspiration: feeling that the subject might not be entirely closed,

they egged on the authorities to set up a permanent and very minute laboratory and to keep Christiaan Eijkman down there to run it.

Up to that point, Eijkman had looked upon the Royal Commission for Beriberi as a rather dull affair. While his chiefs had been dramatically pursuing some deadly microbe, he had been stuck in a hot laboratory. While they were romantically fighting death (largely, it must be admitted, in the fetid aroma of the deadhouse), he had been assigned to count red blood cells. While they were battling a plague, he was measuring hemoglobin.

But now he was on his own, and things would be different. Now he would go ahead and find the real microbe that caused beriberi —for he was still positive there was such a germ—and he would get all the glory.

At the age of thirty, then, Christiaan Eijkman became head, director, supervisor, and virtually the only man who did any work at the royal and sweltering *Netherlands Indies Research Laboratory for Bacteriology and Pathological Anatomy.* For nearly two years he muddled, trying to draw some eloquent triumph out of the mute mass of unimportant data he had collected.

"There must be a microbe," he fumed, "but where is it?"

He made more and more blood smears, and he looked in vain for a bacterium or a bacillus or even the merest coccus. He injected sputum and blood and horrible bits of dead tissue into his animals, but his rats and mice and chickens died of everything but beriberi.

Then, on the tenth day of June in 1889, he fell heir to the answer, although he was to struggle for months yet before that answer finally became clear. On that day his little native assistant approached him.

"Tuan," he said, "the new shipment of feed for the chickens has not arrived."

"Don't bother me," muttered Eijkman. "I'm busy. Go and ask the hospital cook. See if he can spare you something."

The assistant slowly ambled around the corner and put the matter up to the cook. The cook considered the problem very care-

fully and then said, "Tell Tuan he can have some of the cooked food the patients do not eat. With the beriberi they have no appetite."

So Eijkman's assistant began the fateful experiment of feeding worthless, dirty chickens on nice, clean, thoroughly polished white rice—on "civilized" food.

On July 10 the chickens had been on the new white-rice diet for exactly a month, and Eijkman wandered through the poultry yard to discover that odd things were going on. Instead of his flock of healthy, fat, perky chickens he saw miserably sick birds who couldn't even stand up straight. Here was a hen lying on her side—here a poor little rooster, his back in such an arch that he looked like a pouter pigeon—and here a thin, emaciated, paralyzed bird that looked all but dead.

"Hey!" cried Eijkman. "What's happened to my chickens?"

The worried assistant shook his head. "I cannot imagine, Tuan," he reported. "This morning I noticed this strange sickness for the first time. Perhaps they are dying?"

"Of course they're dying, you idiot. Curse it all, they've probably caught some infection. Well, try to separate the sick ones and don't let the others get near them."

Day after day the native boy went through the poultry yard, and each time there were a few more chickens which had been stricken by the strange paralysis—by the creeping disease that climbed from legs to wings, from tail to neck to head, that slowly but surely ended in death.

Once or twice a fantastic thought flickered through Eijkman's mind—"Peculiar how much that chicken-paralysis is like the paralysis of beriberi"—but that was obviously silly. Chickens don't get beriberi.

Then on the twentieth of November, the experiment reached its crisis. A newly appointed superintendent of the hospital came on the job and, economy-minded, discovered the deplorable situation in the hospital kitchen.

"I don't care who this Dr. Eijkman is," he exploded. "His

chickens are positively not going to be fed on expensive polished white rice that I buy for sick patients!"

Dr. Eijkman's chickens—or what was left of them—went back to cheap, ordinary chicken food: dirty brown *unpolished* rice.

And the sick, paralyzed birds promptly got well!

In the stuffy little office, Christiaan Eijkman crouched over his desk. "I know that chickens don't get beriberi," he thought, "but if they should get it, they'd look like my sick birds and act like them and die like them. And yet why did some of my chickens get well so suddenly?"

He went back over his records. The chicken disease had run from July to November. The birds had been on the white polished rice from June to November. The food surely must have had something to do with it!

Completely forgetting the beriberi microbe he had sought for so long, he turned to experiments on food. So the birds got sick on polished rice, did they? And they were cured on unpolished rice?

He repeated that foolish experiment a dozen times until he learned that birds eating nothing but polished rice always died from this strange paralysis; and the birds eating crude, dirty unpolished rice or picking their own food out of the garden or the dunghill never got it. He pinned the blame on the rice, naturally enough. Polished rice was deadly; unpolished rice was safe. Well, then, what was the difference between the two? Unpolished rice still had the skin left on each grain—could it be that in the rice-skin there lurked the cure for chicken paralysis?

He mixed up a brew of dirty rice-skins, stuffed it down the gullets of paralyzed chickens. Within four hours, every one was beginning to look better, and by the next morning the whole flock was clucking away in perfect health.

"I've got it!" he rejoiced. "I can cure every paralyzed chicken in the world!" But who cared about paralyzed chickens? What about paralyzed men and women dying from beriberi? After all, no one had proved that beriberi and chicken sickness were the same.

"Don't have to prove it," he thought, "I know it!"

He went to see Adolphe Vorderman, Sanitary Inspector of Java, a tired old medical war horse who had been out in the Indies for thirty years.

"Dr. Vorderman," he announced, "I have found what causes beriberi. And I can cure it."

"Yah? They always tell me that. First it was arsenic that caused beriberi, then it was oxalic acid, and then it was a microbe. They all know how to cure it, but the people still die by the thousands. Well, my young friend, what is your idea?"

"Rice! They get beriberi by eating the wrong kind of rice, the polished kind. I can cure them by using unpolished rice!"

"My, my! You don't tell me! So now it is rice. How do you know all this? How many patients have you cured?"

"Patients?" Eijkman hesitated. "Well, I haven't tried any patients yet. I've been using chickens. . . ."

Vorderman turned slightly red. "Ah, you have been using chickens. Young man, I am not interested in chickens; I am interested in human beings."

"I'm sure you are," Eijkman conceded, "but I want you to see my chickens. You must see them, please."

Very much against his sober Dutch judgment, old Dr. Vorderman went around to see Eijkman's experiments. He saw the birds dying, and he saw them cured with a little extract of rice-skins. He studied the bodies of birds who got no rice hulls and compared them with the bodies of men dead of beriberi. Finally, carried away by the exuberance of the young researcher, he agreed to take part in a wild experiment. "My goodness," he admitted, "for thirty years I have practiced medicine; now this mad Eijkman makes me a scientist."

The two men began stalking beriberi in the native prisons of Java, and with a few dubious helpers they covered every prison in the islands. "What kind of rice do you serve in your jail?" they asked. "How many cases of beriberi did you have here last year? Thank you." And off they dashed to the next jail.

Within a few weeks they had accumulated a monstrous conviction against nice white polished rice:

Among 96,530 prisoners on unpolished rice—9 cases of beriberi.

Among 150,226 prisoners on polished rice—4,200 cases of beriberi.

In one jail where the prisoners were fed the whitest, most expensive rice, the beriberi was most appalling. "It's so bad here," the head jailer admitted, "that a jail sentence of three months is actually the death penalty. . . ."

Now all those fearful deaths in the Achin War became understandable when the scientists found the little Achinese warriors ate only unpolished rice while the Dutch army got polished rice —and beriberi.

Here was proof so strong and convincing no one could dispute its meaning. And when Eijkman added his discovery that a little brew of rice-skins would cure human patients of their beriberi, his case was complete.

"Wait!" cried the usual little group of glory-hunters. "We wrote years ago that beriberi was caused by bad diets."

"Sure," said Eijkman, "you wrote it—but I proved it!"

Before he could complete his work and see its wondrous effects in the tropics, he fell sick from malaria and returned to Holland. Thirty years later, in 1929, the scientific world thanked him for detecting the first vitamin-deficiency disease and awarded him the Nobel prize in medicine.

While Eijkman had been in the thick of this work at Batavia, young Dr. Gerrit Grijns had been sent out from Utrecht to help him. When Eijkman left the Indies, Grijns was assigned to carry on the beriberi work.

Eijkman had found rice-skins would prevent or cure beriberi, but he didn't know how. "Perhaps," he conjectured, "there is a poison in the rice-grain that causes beriberi. Perhaps the rice-skin contains the antidote."

It was a nice bit of rationalization, for medical scientists at the

turn of the century had convinced themselves only two things could cause disease—a microbe or a poison. If it wasn't a microbe that produced beriberi, Eijkman thought, then it must automatically be concluded that a poison did the dirty work.

But in two years, Grijns showed his chief's theory was completely wrong. He proved in precise, airtight experiments neither a bug nor a poison was to blame. Beriberi was the result of a deficiency—*of a lack of some substance the body must have.*

That substance was already known to exist in the skins of rice. Grijns now proceeded to find it in other foods. Furthermore, he showed beriberi could be produced without bothering with rice at all—merely by using pure diets of sago or tapioca or overcooked meat.

"It's not what you eat that causes beriberi," he declared. "It's what you don't eat!"

Eijkman and Grijns had both done a grand job of research, but they made one costly mistake. They wrote and published their articles not in English, French, or German, but in Dutch—and nobody read Dutch but the Dutch. That mistake cost the lives of untold tens of thousands—men, women, and children who might have lived if only the Eijkman-Grijns reports had been published in another language.

Just a handful of scientists knew about the splendid work that had been done—a few men who happened to visit the Indies and meet Eijkman and Grijns. The great discovery came perilously close to total obscurity. Fortunately, however, the Malay Peninsula was only a few miles from the Dutch East Indies, and in Malaya there was much beriberi.

Across the Malacca Straits from the island of Sumatra is Kuala Lumpur, capital of the Malay States. There in 1905, an outbreak of beriberi ripped through the insane asylum, attacked nearly half the patients, and killed one in every eight. One day, Dr. William Fletcher strode into the asylum and ordered the fifty-nine remaining lunatics lined up in the dining-shed. They were counted off; all the even numbers were marched to the west ward where a diet of

unpolished rice awaited them, while the odd numbers went to the east ward and their usual diet of white polished rice. As new inmates arrived at the asylum, they were assigned alternately to the two test wards.

A year later, Dr. Fletcher counted up the results: in the west ward where unpolished rice was the daily fare, there had been no new cases of beriberi and no deaths; in the east ward where polished rice was served, there had been thirty-four cases of beriberi and eighteen deaths.

It was a nice, clean experiment that wouldn't have been permitted in any well-run European hospital, but its results—however obtained—were indisputable. Concluded Dr. Fletcher: "This fellow Eijkman knows what he's talking about!"

The following year, another batch of human guinea pigs added still further proof. South of Kuala Lumpur, in a remote part of Negri Sembilan, three hundred indentured Javanese laborers were building a magnificent highway. Drs. Henry Fraser and A. T. Stanton divided the men into two camps, gave one polished, and the other unpolished, rice. In less than two months, Camp A on polished rice reported twenty cases of beriberi; Camp B had none. Next the doctors cleverly reversed diets. Immediately Camp A's patients recovered, and soon Camp B reported an outbreak.

Now Dr. Fletcher, working in the insane asylum, and Drs. Fraser and Stanton, out in the road camps, were English doctors. When they wrote their reports, they wrote in English and published them in the chief British medical journals. Their reports were read, and Eijkman—whose name had been bright only in the East Indies—became an international hero.

Soon the whole world knew that beriberi could be prevented and cured—that some diseases were caused by neither a microbe nor a poison but by the deficiency of vitally needed substances.

But what were these substances? What was the magic in rice-skins that could cure beriberi?

In Europe, at the Hamburg Institute for Tropical Hygiene, one Dr. Schaumann did a fine bit of theorizing. "Rice-skins are rich in

phosphorus," he said. "Phosphorus must therefore cure beriberi. Yeast is also rich in phosphorus compounds, and I have now found yeast will cure beriberi patients. It is proved, consequently, phosphorus is the solution. . . ."

But poor Dr. Schaumann was dreadfully illogical. All the phosphorus in the world couldn't cure beriberi; rice-skins worked and so did yeast because both contained another substance—a specific cure for the disease. Nevertheless, his unscientific report catapulted yeast into the medical limelight and from there into big business; some people would soon claim yeast could cure anything.

The real explanation came from a twenty-seven-year-old genius, a Polish chemist by the name of Casimir Funk. He was born the year Eijkman first went to Java; he graduated from a Swiss school when Grijns was playing with sago and tapioca; he was working in the Pasteur Institute while Malayan lunatics were dying in the name of research. He had held an unimportant little position in a German town hospital and had worked with the great German chemists, Fischer and Abderhalden.

In 1911, he was taken on at the Lister Institute in London. "Dr. Funk," said Director Charles Martin, "naturally the choice of your studies here will be left to you; however, I should like to call your attention to an investigation which seems exceedingly significant. Here are some reports on beriberi sent us by our people down in Malaya. Here are the data on some tests in a lunatic asylum and a road camp down there. And here I have a packet of rice-polishings, which are believed to cure beriberi. Perhaps you might be interested. . . ."

Casimir Funk began by feeding pigeons on a diet that produced beriberi paralysis. Then he cured them with rice-polishings and with yeast. So far, so good.

Then, after separating the rice-polishings and the yeast into their different components, he tested each component on his paralyzed birds. It was a job that might easily have taken five years. In four months, Casimir Funk came up with the answer. Out of 836 pounds

of rice-polishings he had extracted 6 ounces of impure, but tremendously potent, crystals.

"Here is the stuff that cures beriberi," he told Dr. Martin. "About one-thousandth of an ounce will cure a paralyzed pigeon in three hours."

"Amazing, my boy!" Martin declared. "What is this—this 'stuff' of yours?"

"I am not certain, Dr. Martin. I know it contains no phosphorus, so that man Schaumann is wrong. I think it is an amine-type compound."

"Ah, and what do you intend to call it?"

"Well, for the sake of simplicity, I think it should be called tentatively the beriberi 'vital-amine,' which might be shortened to 'vitamine.' "

(It wasn't a typical amine at all, but the name—minus the final *e*—was retained from then on as *vitamin.*)

And then Funk made a guess that marks an all-time high for accurate intuition. "You know, Dr. Martin," he added, "I believe there must be other 'vitamines' which will cure other diseases."

Dr. Martin's eyes opened a bit wider. "Do you, Funk? Which diseases do you suggest?"

The answer came at once, "Scurvy, rickets, and pellagra, sir."

Young Casimir Funk had hit the bull's-eye!

II

Funk's first guess was confirmed in less than a year.

One of the men who had visited Eijkman's laboratory was Professor Axel Holst of the University of Christiania in Norway. He had watched paralyzed chickens cured in a few hours with a soup made from rice-polishings.

"This is the most stupendous experiment I have ever witnessed," he declared. "It is the beginning of a new science. I must try it myself."

Seething with new ideas, he returned to his Norwegian labora-

tory and with Dr. Theodor Frøhlich started to repeat the Dutch experiments on beriberi. At the very outset, they made a wonderful mistake. "Let's not use chickens as the Dutch did," they said. "Instead, suppose we use a mammal more like human beings. Let's use guinea pigs."

They did use guinea pigs and stuffed them with overcooked cereal, just the sort of diet that would have paralyzed chickens within a few weeks. But the confounded guinea pigs did not become paralyzed; instead, their gums became sore, their teeth fell out, and evil little hemorrhages purpled their skins.

"This is even more amazing," observed the Norwegians. "These beasts haven't got beriberi—they've got *scurvy!*"

It certainly was scurvy. Guinea pigs, it seemed, don't get beriberi; and Holst and Frøhlich had discovered this by the sheerest accident. But what was the difference? So long as the fates had given them scurvy to work on, they might just as well seek a cure for it.

By adding other foodstuffs to this deadly basic diet of pure overcooked grains, they found that cure. They found it in fresh turnips and carrots and dandelions; they found it in fresh cabbage and raw potatoes; and particularly, as any superstitious sea captain might have told them, they found it in raw citrus fruits.

Scurvy was as old as the art of sailing. It was known only too well as "The Plague of the Sea and the Spoyle of Mariners," for sea diets aren't overly rich in fresh fruits and vegetables. Scurvy had killed two-thirds of Vasco da Gama's crew off the coast of Africa; it had laid a deadly curse on Magellan's men; it had won bloody mention by Francis Drake. Every nation, every war, every ship knew scurvy.

Old Jacques Cartier learned one remedy from Saint Lawrence River Indians—an infusion of fresh pine needles. Two centuries later, in 1747, Dr. James Lind learned that lemons or limes (he didn't know the difference between them) were even better, and by adding limes to the British naval menu, he handed British sailors the everlasting label of "limeys."

Scurvy might have been wiped out right there, but most seamen got the idea that lime or lemon juice would keep better on long voyages if it were heated first. And, unfortunately, the magic properties of these juices are completely destroyed by heat!

Then the two Norwegians, Holst and Frøhlich, showed on their guinea pigs that scurvy, just like beriberi, is not due to a microbe or a poison. They showed scurvy is caused by a lack of a vital substance contained in limes, lemons, cabbage, and a host of fresh fruits and vegetables. And finally they proved this vital substance is destroyed by too enthusiastic heating—and, thereby, they rediscovered the cure for scurvy.

Meanwhile, in half a dozen different laboratories, other men were moving toward the vitamin mystery from an entirely different angle. These were the theoretical scientists, the hairsplitters, the workers whose chemicals must be the purest and whose animals the very best.

These men weren't trying to cure diseases.

These men were developing the science of nutrition.

Developing? Well, that wasn't quite the word. *Perfecting* would be better, or *completing,* or some other word that would denote finality. They had begun to feel they were nearing the end of the trail. They had practically finished the study of nutrition.

"We shouldn't talk about beefsteak," they said. "That is too ambiguous. We should describe that piece of meat in terms of the chemicals it contains—so many grams of protein and so many grams of fat, so many milligrams of mineral salts, and so on. . . ."

Well, why not? Wasn't that piece of steak nutritious solely because it consisted of so many grams of protein and so much fat?

"Of course!" these theorists assured each other. "And we can prove it—we can make the purest of pure diets; we can put in exactly the right weight of the purest carbohydrates, exactly the right weight of the purest protein and fat, and then add exactly the right weight of the proper mineral salts."

This began to look like the diet to end all diets. It would be absolutely perfect. It would be put together to meet every animal

requirement. It would make superanimals out of the scrawniest little laboratory mice.

That's what it should have done, but it didn't. It killed the beasts!

The scientists wailed. "They can't die! Isn't this the best diet ever conceived? Don't we know what's good for animals?"

The mice, dying on synthetic beefsteak, didn't think so.

In Holland, old Dr. Pekelharing, Eijkman's former chief, sadly admitted something had gone wrong. "During the first few days, all went well," he reported. "The mice ate eagerly and looked healthy. But soon they grew thinner, their appetites diminished, and in four weeks they all were dead."

In Switzerland, Dr. Lunin shook his head despondently. "That's exactly what I found," he said.

And in England, Frederick Gowland Hopkins announced the same results. "But it's odd," he added, "that the less pure the chemicals, the longer my animals lived."

All of them agreed "no animal can live upon a mixture of pure protein, fat, and carbohydrate, plus the necessary mineral salts." (Just what Eijkman could have told them, but they paid no attention to him.)

All these scientists also agreed—and this was of greatest significance—these artificial diets became much more healthful *if just a few drops of fresh milk were added.* Therefore there must be something in fresh milk that animals needed for life—something that wasn't protein, fat, carbohydrate, or mineral.

Now—*what was this magic in milk?*

In America, at the University of Wisconsin, Assistant Professor Elmer Verner McCollum proposed a ridiculous but apparently sound explanation. "Flavor!" he said. "That's what the milk adds—flavor! That artificial diet is tasteless and flat, and the animals won't touch it. But just add some flavor, and everything will be all right."

Now Dr. McCollum was no ordinary scientist. He had his Ph.D. degree and all the rest of the trimmings, but underneath he was still a farm boy with all the knowledge that boyhood on a Kansas

farm had given him. And when scientist McCollum put forth the idea of flavor, farmer McCollum sat back to chew on a mental straw.

"Flavor? Perhaps, but maybe it's something else," he mused. "Plenty of feed that looked good to me the animals wouldn't touch! How do I know what tastes good to a cow or a mouse or a rat?"

So he raised rats by the dozens in big packing cases and engaged energetic little Marguerite Davis to take care of them. He fed the beasts on the best diets chemistry could devise and watched them as they refused to eat, as their weight dropped, as they sickened and died. And he noted that, in the early stages of their starvation, their eyes became red and dry and sore.

It was tricky experimenting, since the Authorities, particularly those inquisitive committees from the state legislature, didn't understand why tax money should be wasted to feed rats on pure and expensive diets. "Hell's fire, young man, we can't see any sense in those tests of yours. Isn't there enough good grain in the state of Wisconsin without your trying to find victuals in a test tube?"

But McCollum and Miss Davis didn't know what they were trying to find. . . . Perhaps it was something in milk, something that was a flavor . . . and perhaps it wasn't.

After two years of this teamwork, Casimir Funk's brilliant report on the beriberi "vitamine" came to Wisconsin; nobody paid any attention to it. Another year passed, and McCollum tried in vain to do something about the eye sores that were wrecking his animals. Finally he came upon the first clue that started him up the right path.

"Whole milk will cure the sore eyes in my animals," he reported, "but most of the different parts of milk are useless."

Milk sugar wouldn't cure them, and milk protein wouldn't, and the milk minerals wouldn't. The only part that worked was the milk fat, the butterfat, and that worked every time.

"Well, that's simple," they told McCollum. "You just didn't have enough fat in your diets. That's what wrecked your rats."

"Maybe so," he agreed. He tried the fat from egg yolk and that,

too, helped his animals. Yes, that must be the explanation—not enough fat. Then he tried pork fat and vegetable fats and lard—and not one of them worked!

"Hold on," he said. "There's something funny here. My animals weren't short of fats. They were lacking *certain* fats." And he wrote a report announcing, "There is something in butterfat and egg fat that doesn't occur in other fats. It is a growth stimulant and protects the eyes of my animals." Then, since he finally figured Casimir Funk, who had now come to the United States, might have been right, he added: "To this 'something' I am giving the name of a vitamin—vitamin A."

(Thus the beriberi vitamin, which had been discovered long before, was nosed out of official first place and called vitamin B.)

Within a few months, McCollum's vitamin A went to work fighting disease in men. The Red Cross, battling famine in the Balkans, found thousands of children suffering from "sore eyes," the same kind of sore eyes that had plagued the Wisconsin rats; and foodstuffs rich in vitamin A—butter, eggs, and particularly cod-liver oil—were rushed to work a miracle.

In Denmark, where dairy supplies had all been exported to feed Europe's armies, there was a tremendous outbreak of "sore eyes" and "night blindness." Again the vitamin-A foods came to the rescue.

The war brought vitamin B out of the tropics, too, to cure outbreaks of beriberi in Germany, Austria, Poland, Russia, and the Balkans.

And even the antiscurvy substance, now known as vitamin C, was called in to smash scurvy epidemics in the devastated war zones.

So the world heard about three vitamins—mysterious "things" that came wrapped up in some foods and were absent from others; "things" vitally needed every day by every human being. Europeans learned about them firsthand. Americans waited for Elmer McCollum's next triumph.

McCollum had left Wisconsin, even before the war ended, for

the great new school of hygiene at Johns Hopkins. Miss Davis was no longer his assistant; in her place had come the equally enthusiastic Nina Simmonds.

Into their laboratory one day walked the distinguished professor of pediatrics, Dr. John Howland. "Know anything about rickets?" he inquired.

"No," answered McCollum. "Why?"

Howland handed him a British medical journal. "Fellow by the name of Edward Mellanby at the University of London has found out how to produce rickets in puppies and how to cure 'em. Better read it yourself."

It didn't take McCollum long to skim through the most exciting report he'd ever seen. The English doctor Mellanby had produced rickets in puppies by feeding them nothing but a little milk and oatmeal porridge. On this diet the poor pups failed to grow, their legs became deformed and weak, their ribs were knobbed, their chests compressed, their spines curved. They acted just like children with rickets—"good" little animals, quiet and lethargic. Actually, very sick little animals.

Next Mellanby added to the basic diet one foodstuff after another—whole milk, yeast, malt, butter, linseed oil (highly praised in London as a sure cure for rickets), peanut oil, olive oil, orange juice, and dozens of others. None of these had the least effect: the puppies lay quietly, deformed and sick, until they died.

And then he gave other rickety pups some cod-liver oil. Why? Well, perhaps because there was an old Norwegian legend that cod-liver oil was good for babies, and perhaps because a few unprogressive, unscientific baby doctors thought it had merit. And cod-liver oil, he found, was spectacular for his ricket-crushed puppies. Their warped bones became straight and strong, and their broken spirits were mended. They became frisky, pesky young hellions of dogs.

Cod-liver oil did that—or rather a "something" in the oil, a "something" that Mellanby had also detected in butterfat.

"Say!" cried the excited McCollum. "In cod-liver oil and in

butterfat, eh? Plenty of vitamin A in both. . . . Could it be vitamin A that cures rickets?"

"I'm sure I haven't the faintest idea," Howland replied, "but there certainly are a lot of us who'd like to know. We're seeing too many babies whose bones are shot with rickets, whose teeth are no good, who haven't any resistance to infections. I tell you, McCollum, if you find out Mellanby is right—that cod-liver oil is good—we're going to use an awful lot of it!"

McCollum and Miss Simmonds dropped all other work to consider this new problem. Now that Mellanby had published his findings, they recalled that they, too, had seen the odd "nobby ribs" in their experimental rats. Could cod-liver oil protect their rats from such changes? Could cod-liver oil do it *after* its vitamin A had been removed?

There wasn't a drop of cod-liver oil in the hospital, where too many children were lying crippled from rickets. Nina Simmonds flung on a coat and ran to a drugstore on the next block. "Do you have any cod-liver oil?" she asked.

The druggist peered at her. "What d'you want that stuff for? Oh, for rickets. . . . Heck, that's no good. Better take some of this olive oil. It's seventy-nine cents special today."

"No, thanks," said Miss Simmonds, "please let me have the cod-liver oil." The druggist shrugged and wrapped it for her.

Back in the laboratory, the scientists made ready to tear that oil to pieces. "We'll heat it and bubble oxygen through it at the same time," said Dr. McCollum. "That'll destroy every bit of vitaman A."

Miss Simmonds nodded. "And if the cod-liver oil can prevent rickets, then we'll know there's something else in there—something potent besides A. . . ."

For twenty long hours, they kept a beaker of cod-liver oil heated nearly to boiling and passed oxygen through it in big blurbing bubbles. They kept it running until the vitamin A was all gone, until it no longer had the power to cure "sore eyes." Then this half-emasculated oil was given in measured drops to young rats, and

it protected them from rickets. It could even cure them from rickets.

Next, untreated cod-liver oil was given in even more carefully measured doses to rickety boys and girls, and they got well! It was just what the old Norwegian legend had predicted, but now the scientists had proved it for themselves. They had proved not only that cod-liver oil can cure rickets, but that vitamin A didn't do the curing. It was something else in cod-liver oil, something new.

It seems almost impossible that the scientists spent months and years on this modern miracle before they were convinced. McCollum and Miss Simmonds, with Drs. Park and Shipley of the pediatrics department, worked day and night until every last question was answered. Then, in 1922, came their simple, eloquent announcement:

"We have detected in cod-liver oil the presence of an unidentified substance which prevents and cures rickets. For the present, we are naming it vitamin D."

And so vitamin D was discovered, to save and cure America's children. Book-writing baby specialists who penned learned treatises on the care and feeding of children rushed to include cod-liver oil in their menus. Other scientists learned how to concentrate this mysterious vitamin D and to put it in the form of a nearly pure potent oil—a few drops equivalent in rickets-curing power to pints of fresh fish oil.

It was unquestionably one of the greatest and most practical discoveries of the twentieth century, but instead of clearing up a scientific mystery, it propounded a more confused one. For, in Germany, Dr. Kurt Huldschinsky had reported, "No, it cannot be cod-liver oil that cures rickets—it is sunlight." And Dr. Huldschinsky had proof.

Even before McCollum had started on his hunt for a rickets-cure in cod-liver oil, Huldschinsky had been curing rickets in Berlin children.

Sunlight was an old, effective, though usually not scientifically

acceptable, cure for the bone disease. Generations of doctors had proved rickets is a disease of foggy, northern countries and rarely appears in the tropics. These old practitioners had wisely prescribed sunshiny vacations for growing children. But in the Berlin of 1919, there was neither sunshine nor the money for vacations, nor even the money to buy the cod-liver oil recommended by some old-fashioned and superstitious physicians.

So scar-faced Dr. Huldschinsky, who couldn't send his sick little patients to the sun in Italy or Spain or North Africa, decided to bring the sun to them in Berlin. Didn't the big electric manufacturers advertise their ultraviolet lamps as "sun lamps"?

Under these lamps he placed four of his worst patients—bathing them twice a day, front and back, in the ghastly green-purple glow. In two weeks, right in the middle of winter, their bodies had become tanned; and under this tan, strange things were happening to their bones. In two months the transformation was unmistakable—the four little patients had become strong, healthy, hungry kids. No longer were they weak, whimpering, apathetic; they were so full of spirits and trouble the ward nurse offered to wallop them if they didn't behave. Dr. Huldschinsky reveled in those reports of "badness," for they, plus the X-ray evidence of strengthening bones, proved the rickets had gone.

Now the world had sunlight and particularly ultraviolet light as a specific cure for rickets, and it also had vitamin D in cod-liver oil as a specific cure. Which was the *real* cure?

To find out, the English medical authorities sent five lovely scientific ladies to Vienna, where rickets was widespread and severe. They marched into the University's Kinderklinik and went to work.

Very serious were the English ladies. They divided the patients into three batches. One got cod-liver oil, the second got baths in ultraviolet light, and both groups got well. The third group received no treatment and remained sick and rickety. Thus, the first question was answered again—both ultraviolet light and cod-liver oil could cure the disease.

But the problem was still there. How in the world could a fish oil and rays of light both have the same miraculous properties?

The English women didn't answer that one, but they left the answer buried in their detailed report. Two of them, Eleanor Hume and Hannah Smith, had tried to cure rickets in rats with ultraviolet light, and they had done this very well. They had cured the animals by bathing them with the light just as they had treated the sick children. But they had also cured them by taking them out of their cages and then irradiating the empty cages before putting the animals back.

That second experiment completely baffled the Misses Hume and Smith. It worked very well—but how? How could ultraviolet light cure rickets by being poured on empty animal cages? They didn't know.

In America, two groups of workers picked up that clue and tore into it with scientific frenzy. Dr. Alfred Hess went to work at Columbia University, and Dr. Harry Steenbock started at the University of Wisconsin.

These Americans had picked up a point the English scientists didn't consider very important. The Misses Hume and Smith reported they had irradiated *empty* cages; but were they really empty?—not at all! True, the animals had been taken out, but the cages still contained a few bits of food, a few droppings, a few bits of straw and sawdust and dirt.

The Americans knew the habits of rats, knew these beasts do not have the best of table manners, knew they would nibble at those old droppings and bits of dirt. *And these things had been left in the cages during the ultraviolet baths!*

Wisconsin's Steenbock went to work in November of 1923, and on April 18, 1924, his report reached the editors of the *Journal of Biological Chemistry.* He, with Archie Black, reported the discovery that the power of sunlight, the power of ultraviolet light, had been trapped in foods. Olive oil and lard, which never in a thousand years could have cured rickets on their own, had been treated with ultraviolet light and turned into that cure. Ultraviolet

light had created vitamin D in those foods. The scientists had literally trapped the sun.

That report was received in April of 1924, but only the editors knew about it. Then in June, Hess and his group of New York workers made a public announcement before the American Pediatric Society meeting in Pittsfield, Massachusetts. Hess announced that ultraviolet light could turn cottonseed oil and linseed oil into ricket cures.

The world hailed Hess for a glorious piece of research. People talked of rewards, great honors, perhaps a Nobel prize. And then, four months later, the *Journal of Biological Chemistry* got around to printing Steenbock's report—and at the head of the article was the notation: "Received April 18, 1924."

Steenbock had won out by less than two months, and his university capitalized on that victory by obtaining patents and collecting rich royalties with which to support further research.

Now that the experiments were done, it was no trick to figure out that almost any food—milk, bread, mush, vegetable oils, baby foods, breakfast foods, or chicken feed—could be passed under ultraviolet light and enriched with vitamin D.

Now it could be shown that ultraviolet light and vitamin D were essentially the same, for Hess proved ultraviolet light could produce vitamin D in bits of human skin.

The scientific world, the medical profession, and even the lay public grasped at these findings; for they were important and practical, and they were also highly romantic. That business of the ultraviolet light was just like the stories of the old sorcerers.

Then in 1927, old Christiaan Eijkman, the discoverer of the cure for beriberi, reappeared on the scene and threw sorcery out of the window. From Holland, he made an announcement of tremendous significance. "From my old laboratory in Batavia," he said, "two of my compatriots have sent me a report. Dr. Jansen and Dr. Donath have asked me to announce that they have isolated the beriberi vitamin, vitamin B, in crystal form. *This substance is a pure chemical. . . .*"

Chemical! All over the world, the chemists pricked up their ears. "If vitamins are not mysterious 'somethings' but are actually chemicals," they proclaimed, "this is where we go to work."

III

For the next few years, they did just that, with dazzling success. Working in fifty laboratories, these chemists pitted their merciless analytic methods against the "mysterious vitamins" and turned their mystery into chemical knowledge.

Was vitamin A a romantic, supernatural something? Nonsense, explained the chemists, it's merely a chemical—*3,7-dimethyl-9(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetren-1-ol.*

Complicated? Perhaps, but not half so complicated as a supernatural something.

And vitamin D, that remarkable product of captured sunlight? That, discovered the chemists, is merely activated *7-dehydrocholesterol.*

And so on, right down the list.

The chemists studied all the vitamins that had been found and tore them apart and put them back together until they became as understandable as water or salt. They cleared up the mystery of vitamins A, B, C, D, and E, and finally they bumped into vitamin G.

This substance was so easy to discover it was almost missed. It was known not only as vitamin G, but also as vitamin B_2 or vitamin P-P. It had been found a dozen times and yet always ignored, since it seemed too common to be valuable; and then along came young Dr. Elvejhem.

Conrad Elvejhem was born in 1901 in a little farming town in Wisconsin. In 1919 he went to the University of Wisconsin, and a happy fate guided him to the department of agricultural chemistry—into the hands of E. B. Hart and Harry Steenbock.

In 1923, equipped with a shining new bachelor's degree, he was grabbed by these topnotch hunger-fighters and put to work. "We

mustn't let this fellow get away," they agreed, "he's got something!"

So Elvejhem became an assistant agricultural chemist.

He was first assigned to work with Professor Hart on chicken diets (and how important that work was going to be!) and then on vitamin D and on anemia. In 1929 he was given a fellowship at the University of Cambridge and went over to compare notes with the top hunger-fighters in England. Then he returned to Wisconsin as an assistant professor and took up a new job. He decided to take a crack at pellagra.

Pellagra was a food sickness, one of the worst of all the deficiency diseases. For two centuries, doctors had battled it all over Europe. In the southern part of the United States, it crippled a quarter of a million, killed more than ten thousand victims a year.

Pellagra started like a bad case of sunburn, with peeling and blistering. Then the skin turned rough and brown, scaling and shredding. Patients were marked by skin sores, mouth sores, tongue sores, and finally disintegration of the brain.

Long before Elvejhem went to work on it, Hungarian-born Joseph Goldberger of the United States Public Health Service had proved that pellagra was a food disease. Like the scientists before him, Goldberger had been told that pellagra was caused by a microbe, but unlike his predecessors, he refused to believe it.

"A germ disease? Impossible!" he declared. "How could it be caused by germs when it never attacks the doctors and nurses in pellagra hospitals?"

In fearful, dramatic tests, he even proved there was no germ to blame. He took bits of pellagrous skin and ate them—and his wife ate them. He took pellagrous blood and injected it into himself—and into his wife. Neither he nor Mrs. Goldberger caught pellagra. The disease, he concluded, was not microbe-borne.

Instead, he proved with convicts at Mississippi's Rankin Prison Farm that it was caused by diet—particularly by the typical southern "white trash" diet of too much salt pork, molasses, and corn meal and not enough lean meat, milk, and fresh vegetables. And

finally he proved pellagra could be prevented or cured by a substance he had tracked down to liver and yeast.

This same mysterious substance, he found, also cured a disease in dogs known as blacktongue.

When he died of cancer, much too young, all he knew about this substance was that it was present in some foods, that its exact properties were unknown, that it was tentatively called vitamin B_2 or vitamin P-P (for pellagra-preventive) or vitamin G.

Conrad Elvejhem, now returned to Wisconsin, knew the same things and practically nothing more; but he had worked with liver extract before, so he concentrated on finding why liver cured pellagra.

He needed subjects for experimentation and looked around for pellagrous patients, but Wisconsin didn't have any. He asked for dogs in which he could produce blacktongue, but dogs were too expensive. He tried to rig up a diet which would produce pellagra in rats, but the rats remained disgustingly healthy. In desperation he turned to chickens, and in them he succeeded in producing a nasty pellagra-like disease, a disease quickly cured by whole liver.

Now, what part of the liver, what particular chemical, did the actual curing?

Certain that one of these substances—undoubtedly it would be a brand-new, highly complicated compound—could cure his birds, he broke liver down into its different components. But when he finally found an active liver extract, its chief ingredient was no new, complex chemical.

"Why, it's merely nicotinic acid," he grunted. "That stuff couldn't be a vitamin—it's too simple!"

Nicotinic acid was a simple chemical, sure enough, known to generations of chemists as a thoroughly useless compound. It had been discovered sixty years before as an oxidation product of nicotine. Casimir Funk found it in yeast extract and thought it might be of some importance. A couple of Japanese workers found it in rice-polishings. It had even been tested on beriberi and found, to nobody's surprise, completely ineffective.

But Conrad Elvejhem couldn't ignore nicotinic acid. The fact that everyone else had dismissed it as valueless didn't make it so.

It was no time now to worry about expense. He got some dogs, put them on one of those deadly purified diets, and waited until they were almost dead of blacktongue. Under their skins he injected tiny doses of the purest nicotinic acid he could buy from the Eastman Kodak Company, which had bottles and bottles of it collecting dust on their shelves, and sat down to see what would happen.

What he saw sent samples of nicotinic acid posthaste to Indiana two weeks later, where physicians were cursing one of the craziest outbreaks of pellagra in history.

There had been a social worker in Indiana, a very sympathetic fellow who spent his days trying to cure the financial ills of his clients. That would have been safe enough, but he went still further—he spent his nights thinking up economical diets for his people, and his diet was an excellent pellagra-producer!

Four of these pellagra victims were admitted to the hospital and put under the care of Drs. Paul Fouts and Oscar Helmer. After a three-day test period to be sure the patients weren't getting any better by themselves, the doctors started the nicotinic acid treatment. The acid was given by mouth, and the patients made only one comment—within ten minutes, they said, "Gee, Doc, my skin feels funny, sort of hot and tingling."

Within forty-eight hours, they had more and different things to say. The sore mouths were healing, the skin sores were getting better, upset stomachs were normal, and the strange "mental attitude," the first sign of impending insanity, had vanished.

Less than a month after the Indiana report was set before the public, the Eastman Kodak stores of nicotinic acid were absolutely depleted. In fact, nobody had any left, and there were immense heaps of orders arriving in every mail. New Orleans wanted nicotinic acid, pounds of it. Atlanta wanted it. So did Galveston and Charleston and Savannah and Saint Louis. It was a godsend—and

amazingly cheap. The complete treatment for one patient cost about ten cents.

Now that the pellagra-preventive had been identified as nicotinic acid, the chemists had a strikingly complete "who's who" of the chief vitamins. Vitamin A, the anti-night-blindness and anti-sore-eyes substance, had been practically isolated by Steenbock at Wisconsin, studied by von Euler at Stockholm, and its formula determined by Karrer, one of Paul Ehrlich's students, in Switzerland. It was synthesized in 1947 by Arens and van Dorp in Holland. Science said "thanks" by awarding Nobel prizes to von Euler and Karrer.

Vitamin B was found to be a meaningless term, covering a multitude of substances, and was divided into B_1, B_2, B_3, and so on. It was B_1 which cured beriberi and other diseases of the nervous system. Jansen and Donath down in Java had isolated it, and Windaus in Germany almost worked out its formula. The job was finally completed by Robert Williams of the Bell Telephone Laboratories in New York; he synthesized vitamin B_1 under the name of *thiamin,* thanks in part to an armchair theory worked out by a couple of Japanese and a lucky laboratory accident.

Vitamin B_2, which cures a few minor diseases in man and animals, was isolated from milk by brilliant young Richard Kuhn in Germany and synthesized under the name of *riboflavin* by Kuhn and Karrer of Switzerland. Nobel prize to Kuhn.

Folic acid, another member of the B family, was developed as an inexpensive and easy-to-take partial substitute for liver extract in the treatment of various macrocytic or "big-cell" anemias, including pernicious anemia, goat's-milk anemia, noninfectious sprue, and pernicious anemia of pregnancy. It was isolated from spinach, alfalfa, and tree leaves by workers at the Universities of Wisconsin and Texas, prepared in pure crystalline form by J. J. Pfiffner and his group at the Parke, Davis Laboratories, and synthesized by Coy Waller at the Lederle Laboratories.

Vitamin C, the answer to scurvy, was isolated from lemons by Charles King and W. A. Waugh at Pittsburgh, identified by Szent-Györgyi in Hungary, and synthesized under the name of *cevitamic acid* or *ascorbic acid* by Reichstein in Switzerland. Nobel prize to Szent-Györgyi.

Vitamin D, the remarkably potent antirickets chemical known as *7-dehydro-cholesterol,* was isolated by Windaus in Germany, together with workers in England, Holland, and the United States. It was Windaus who determined its formula and won the Nobel prize.

Vitamin E, necessary for normal reproduction and healthy muscles, was first detected and then isolated from wheat-germ oil by Herbert Evans in California and given the new name of *alpha-tocopherol.* Its formula was worked out by Fernholz in New Jersey, and the synthesis was completed by Karrer in Switzerland.

Vitamin K, found in alfalfa and rotting sardine meal, a preventive for a deadly form of hemorrhage in newborn babies and in jaundice victims, was discovered simultaneously by H. J. Almquist in California and by Dam and Schønheyder in Denmark. It was synthesized as *2-methyl-3-phytyl-1,4-naphthoquinone* by, Almquist and almost at the same time by L. I. Fieser of Harvard and Edward Doisy of Saint Louis. A Nobel prize jointly to Dam and Doisy.

Vitamin P-P, the pellagra-preventive, was identified as *nicotinic acid* by Elvejhem of Wisconsin.

In addition, a Nobel award had been divided between Christiaan Eijkman and Sir Frederick Gowland Hopkins for general all-round service in the vitamin field.

The score: nine vitamins stripped of their mystery, seven Nobel prizes awarded the strippers. There are still other vitamins that have been synthesized—pantothenic acid, pyridoxin, and other forms of vitamins D, E, and K. There are even more substances listed as borderline vitamins, awaiting further investigation. And there are undoubtedly more vitamins which haven't even been detected. The vitamin-hunters have just started.

Pure 7-dehydro-cholesterol isn't the final answer to rickets, and pure nicotinic acid isn't the solution of pellagra. All the vitamin-hunters emphasize this, just as they emphasize the fact that the other pure vitamins aren't the final answers to the diseases they control.

For the vast bulk of the population, those vitamin diseases can be most effectively controlled by intelligent diet—by eating the foods that contain vitamins, naturally or otherwise. But for people who are sick or dying because of unintelligent diets or inability to secure proper foods, the synthetic vitamins have a value that cannot be measured. For such victims the vitamins are not foodstuffs—they are drugs, pure chemicals with known formulas. They are medicines that can be administered in carefully measured doses to produce exactly the desired effects. They are potent weapons against the most terrible of the hunger-deaths.

Down in the hot, rain-drenched city of Batavia is the little laboratory where all this vitamin-hunting began. In 1938, it celebrated its fiftieth anniversary by dropping its old name of *Netherlands Indies Research Laboratory for Bacteriology and Pathological Anatomy.* Its new title proves that sometimes a prophet may be honored even in his own country. The new name is simply the *Eijkman Institute.*

CHAPTER IX

Magnificent Trifles

BROWN-SÉQUARD AND THE HORMONES

"BY JOVE, Captain, you haven't wasted any time."

Captain Brown shook his head. "Too many lives depend upon my speed, Mr. Travis. There's a famine back in Mauritius. They sent me here to India for this rice; if I don't get it back, and quick too, there's a powerful lot of people won't live very long."

"Well, I say, you've certainly done your part. Many thanks for the order, Captain, and a good voyage to you."

"Thanks to you, Mr. Travis." The tall American captain shook hands and waved farewell. Then Travis called again. "Say, Captain, how's that beautiful wife of yours?"

"Fine, just fine. Going to present me with a son and heir in a couple of months. . . ."

Three thousand miles to the south, on the island of Mauritius in the Indian Ocean, they waited for Captain Edward Brown and his ship, for that cargo of rice to prevent impending famine. Weeks went by, and the food shortage became more acute. Starvation began to wreak its havoc on the people, and there was no sign of the ship. More weeks passed, and the famine reached its peak; still no word from Captain Brown—merely rumors of hurricanes and of pirates sweeping out of the Bay of Bengal into the Indian Ocean.

On April 8, 1817, with her husband given up for lost, Henriette Séquard Brown gave birth to a son—Charles Édouard Brown.

Son of a Philadelphia sea captain and a beautiful French mother, Charles early in life tacked his mother's name on to his own to

make it Brown-Séquard. It was a name that would be known throughout the world as that of one of the most brilliant, erratic scientists in history.

From the ill-fated day he left India, Captain Brown was never heard of again. His widow was forced to support herself and her young son by sewing and embroidering. By the time he was fifteen, Charles helped by clerking in a little Mauritius shop. At night, however, mother and son dreamed of days when the world would honor the name of Brown-Séquard; Charles was planning to become a very great writer.

When Charles was twenty-one, he and his mother went to Paris, and there he laid a stack of manuscripts—poetry, novels, and plays—on the desk of a Parisian literary critic. Within half an hour, Brown-Séquard had his answer.

"Monsieur," said the critic, "it would be cruel of me to indicate you have talent. You have not. I should suggest you learn a trade or go into business."

If the world of literature did not want Brown-Séquard, then neither did he want either a trade or a business. He compromised by studying medicine and eight years later received his doctor's diploma. For the next forty years, he was almost a fabulous legend to doctors on three continents.

He practiced medicine in Paris and helped the immortal Claude Bernard found the Society of Biology. He subjected himself to weird experiments—wrecking his stomach by swallowing sponges to absorb the stomach juices and then pulling out the sponges with a long wire. He fought cholera in his old home in Mauritius and battled with monarchistic authorities in Paris.

He fled from France, a political refugee, and came to America—on a slow sailing vessel so he might have time enough to learn English. In the United States, he taught French and practiced obstetrics, at five dollars a delivery, in New York. He taught at the University of Virginia and was thrown out because of his unorthodox views on slavery. He married the niece of Daniel Webster and took her back to France.

In Europe again, he started a Parisian medical journal which got him into trouble, directed a big hospital for the insane in London, became a professor at Harvard University, started a few more ill-starred scientific magazines, lectured at the school of medicine in Paris, and won medals by the bucketful.

When his first wife died, he married again; when his second died, he married a third.

He commuted between Europe and America nearly sixty times, popping in and out of hospitals, universities, laboratories, and scientific meetings. He looked like a giant, bewhiskered beetle. He always had something to say, and he always said it. And when he talked, which was nine-tenths of the time, his medical colleagues always listened.

During this hectic career, Brown-Séquard had bumped into a baffling question—one question he did not discuss. "Why do men get old?" he wondered. "And when they get old, why do they grow weak?"

As the years rushed by, he fashioned himself an answer: "Why do we grow old and weak? Because of a natural series of organic changes and because the spermatic glands, the testes, gradually diminish in activity."

In 1875, when his colleagues weren't looking, Brown-Séquard crept away to the little town of Nahant, near Boston, and collected a dozen decrepit old dogs. Into their flabby, dry skins he injected an extract prepared from the testes of healthy young guinea pigs.

Eleven of the dogs showed not the slightest effect. In the twelfth?—Brown-Séquard wasn't sure, but he thought he detected the first signs of rejuvenation, of regained vitality. It was an experiment, however, that was not repeated; even Brown-Séquard, with all his disregard of the proprieties, didn't dare go too far. . . .

Fourteen years passed, but he never forgot that experiment and that twelfth dog—the animal that seemed to get a little younger. Then, in 1889, Brown-Séquard celebrated his seventy-second birthday and realized even he had become an old, old man.

Even at seventy-two, this scientific heretic was still a researcher.

Even when he could hardly stand, he spent every possible minute in his laboratory. And then he decided he must find out, before it was too late, whether that twelfth dog had actually benefited—*he must find out on himself!*

In his Parisian laboratory, he tried the test again to check its safety, this time using senile rabbits. The treatment seemed perfectly harmless, and the rabbits seemed to improve. With this assurance, he commenced a series on himself. Over a period of three weeks he gave himself ten injections. At first he used testicular material obtained from young dogs in the prime of life; later he took his extract from young guinea pigs.

On June 1, 1889—a memorable evening for science—Brown-Séquard stood before the French Society of Biology. The members smiled warmly at this old man—the man who had helped found the society, who was now its president, who was one of the most famous scientists in the world.

"Messieurs," began Brown-Séquard, "I am seventy-two years old. My strength, which had been considerable, has notably and gradually diminished during the last ten or twelve years. Until two weeks ago, I was so weak that I was always compelled to sit down after an hour's work. . . . On returning home, I was so extremely tired that I invariably had to go to bed. Very frequently the exhaustion was so great that, although extremely sleepy, I could not go to sleep for hours. . . . And then I started a series of injections. . . ."

In the audience, the dignified scientists stirred uncomfortably. And as the speaker told them what these injections were, they gasped in scientific horror.

But Brown-Séquard always spoke out, and he would not stop now. "The day after the first subcutaneous injection and still more after the others, messieurs, a radical change took place in me. I regained the strength I possessed many years ago. Laboratory work no longer tired me. I could work after dinner. I could walk easily up and down stairs—without holding to the banisters."

And then he enumerated and described the tests he had performed on himself—matters which should have been too delicate

for discussion—tests to measure the weight he could lift, to measure the propelling force of his bladder, to measure the effects on his constipation.

Finally he told his colleagues he had stopped the treatments and soon had "witnessed a complete return of the state of weakness which existed before the first injection."

He stopped, folded his manuscript, put it in his pocket, and sat down. There was a slight bit of applause which seemed to stifle in embarrassment. There were scattered coughs and faint nervous laughter. Then, "If there is no comment on the paper by Professor Brown-Séquard," remarked the chairman, "we shall continue to the next speaker. . . ."

But Paris and France and the whole world, it seemed, were infinitely more eloquent. Newspapers were filled at once with glowing reports on a new "Elixir of Life." Dissipated old roués poured into Brown-Séquard's consultation rooms. Cartoonists had themselves a holiday, and in Paris the cartoonists were exceedingly clever. Statesmen and economists and many a scientist wrote elaborate articles for the press; some praised the dawn of a new era in medicine, but most scoffed or laughed or screamed in outraged dignity. Most of them indicated, in or between the lines, that poor Brown-Séquard was in his second childhood.

"It is a sad thing," they mourned, "to see such a man as Brown-Séquard, who has done so many splendid things, now becoming senile and ridiculous. . . ."

One benevolent old practitioner in New York pointed out that the injections couldn't possibly have any effect, because there was no reason to explain why they should. "The theory is opposed to all the laws of physiology and chemistry," he burbled. "Further than that, I believe it is a very dangerous proceeding and that it is time for reputable physicians to express their disapproval of the experiments. . . . *Those who have tried it offer no explanation of the result obtained!*"

Other authorities proclaimed, "Its hold on the public is due to a love of the mysterious."

"It is not a new idea. Mention of its use was made three centuries ago."

There were the three time-honored objections: first, it's new and therefore wrong; second, it may be right, but it's not new; third, it may be new and right, but it's not important.

That all started on June 1, 1889. It was the birthday of the hormones. Brown-Séquard was undoubtedly wrong, crazily and ludicrously wrong, but a few men believed him, and they were enough to start a revolution.

II

Now Charles Édouard Brown-Séquard was not the first, by several thousand years, to take an interest in the glands with which every animal body is equipped.

Animal organs had always been used to cure mankind—the brain of the squirrel to treat epilepsy, the brain of the owl for headache, and the brain of the sheep for insomnia. The heart of the deer was recommended for heart disease, the lungs of the fox for tuberculosis, and the liver of the wolf and of the goat for jaundice and dropsy.

Did the patient have fever?—give spleen of the fox.

Was it indigestion?—use the gizzards of chickens.

Did the doctor desire to increase generative powers, to facilitate childbirth, or to cure some disease of the bladder or the reproductive organs?—he should prescribe the testicles of the hare, the deer, the horse, or the pig.

There were many doctors who looked at the thyroid gland in the neck and the pancreas near the stomach, at the ovaries, at the spleen. What did these tissues do? What diseases could they cure? There were others who actually found out what happened when such glands as the testicles were cut out of young male chicks, young male horses, and young male guardians of a sultan's harem.

There was a French doctor, Théophile de Bordeu, who wrote in 1775, "Each organ serves as a factory and laboratory for a specific

humor, which it returns to the blood after having prepared it within itself." But de Bordeu had once been accused of stealing jewels from the bodies of his dead patients, and naturally no one believed what he wrote.

At the University of Göttingen, Professor Berthold cut out the testes from four young male chicks—an operation which invariably resulted in the development of capons, big, fat, sexless birds without comb, wattles, spurs, or cock-a-doodle-doo. But Professor Berthold took the cut-out testes and transplanted them under the skin of his birds, which thereupon developed like normal roosters with comb and crow and all the rest.

He published his findings, but unfortunately in a little journal that didn't have more than two hundred subscribers.

There were dozens, perhaps hundreds, of these ideas and experiments, but none of them received any attention. Then along came Brown-Séquard, and scientists began thinking new thoughts.

Four years after the Brown-Séquard explosion, an English physician crystallized one of these new ideas. He walked into the laboratory of Edward Schaefer in London's University College and introduced himself.

"Professor Schaefer," he said, "my name is George Oliver. Have you ever heard of any substance in the body that frightens people half to death?"

"That does what?" asked Schaefer.

"Frightens them, sir, frightens them! I give a little of this material to a perfectly normal man, and immediately he acts as if he'd seen a ghost—his skin goes white and clammy, his heart begins to beat like a drum, he sweats and trembles, and his blood pressure goes way up."

Schaefer's mouth sagged in amazement. "Eh? He acts like . . . he does, does he? My goodness, sir, what on earth did you give your patient?"

"Fresh adrenal glands," answered Oliver.

So, during the winter months of 1893, Schaefer and Oliver went probing into the adrenal glands, the pair of little organs that perch

like cocked hats on top of the kidneys. Oliver wanted to find an explanation for the fright he noted in his patients; Schaefer sought that, too, but he also looked for the cause of that increase in blood pressure. There didn't seem to be any market for a drug that frightened people, but he could think of many uses for a blood-pressure stimulant.

In six months, they succeeded in preparing a juice from the adrenal glands, a clear liquid that produced all the amazing symptoms given by the whole gland. In Germany, a preparation of this juice was manufactured commercially—one pound of it from the glands of twenty thousand animals. The makers, however, were so apprehensive that they labeled each bottle: *For external use only!*

How that label would change!

Meanwhile, in a Baltimore laboratory, Dr. John Jacob Abel went to work on the adrenals. Born near Cleveland in 1857, Abel had been studying medicine and walking the wards in Vienna when Brown-Séquard had made his speech in Paris. He had returned to America, first to the University of Michigan and then to a professorship in the new school of medicine at Johns Hopkins.

Abel was no stranger to research. He had already studied the spinal cord of frogs and the skin pigments in Negroes, the most odoriferous compounds in urine, and even the concentrated essence of skunk. Then he ran across the report by Schaefer and Oliver.

Within a few months he had his first crude extract from the adrenals of sheep. A year later he had a purer extract, a gray-white powder which he called *epinephrin,* meaning "substance-from-the-gland-upon-the-kidney."

This was still not the pure active substance, and he kept on, trying every chemical trick he knew to purify it. Then one day in the fall of 1900, a commercial chemist from New Jersey, Jokichi Takamine, visited his laboratory.

"You are so exceedingly kind to see me," murmured Dr. Takamine. "I have understood you are studying a substance from the adrenal glands. You have purified this substance?"

"Not entirely," Abel confessed. "We're still working on it. You see, Dr. Takamine, it's very difficult to get the real material out of the glands without going through a long, laborious process."

"Oh, so. What is this process, Professor Abel?"

The Baltimore scientist related the details while Takamine nodded sympathetically. "This is most interesting, Professor Abel. Ah, this epinephrin which you have discovered—do you believe it is possible to find a simpler method to prepare it?"

"Simpler? Sure," said the genial Abel. "We'll probably find some better way any day now."

Takamine smiled. "Of course. Ah, Professor, I enjoy so much to see a seed planted—to see it grow in the technical field. Good-by, Professor, good-by." And he went out—smiling.

Abel stared after the departing Japanese. "Now," he wondered, "what did he mean by all that?"

Abel had clearly underestimated the ingenuity of his visitor. Within a few weeks, Takamine discovered that the actual active ingredient in the adrenals could be purified quickly and cheaply by a little trick—a chemical manipulation worked out a century before by Sertuerner, the little German pharmacist who discovered morphine. Sertuerner had isolated morphine from opium by treating an opium solution with ammonia.

Takamine now isolated his compound from the adrenal glands by adding ammonia to a solution of adrenal juice. In a couple of hours after he poured in the ammonia, a batch of burrlike crystals appeared. This new stuff was patented at once under the name of *adrenalin.*

At Baltimore, there was smoke and fury. Abel's friends were outraged. "That Takamine has tricked you," they told him. "He's patented your discovery!"

Soon Takamine's product was put on the market by a Detroit manufacturer, and immediately other drug-makers, who had no love for their Detroit competitors, rushed to Johns Hopkins with their fists full of money. "Here's a million dollars to fight 'em!" they

roared. "Break that Takamine patent, and you can write your own price!"

But Abel declined the offers. "I made the scientific discovery," he said. "I worked out the process to the point where Dr. Takamine could finish the purification. That's reward enough for me." And he refused to engage in what would assuredly have been a long and bitter legal battle.

It didn't take long for Abel's epinephrin, or Takamine's adrenalin, or whatever it should be called, to show its real value. Within a few years, virtually every practicing physician in the world was employing it. It was used, mixed with novocaine, to give safe and prolonged local anesthesia. It made possible the old dream of near-bloodless surgery. It was used to control hives and hay fever and asthma.

Other workers showed it could be used with sensational results to boost a failing heart, particularly during surgical operations. It became famous to millions of movie-goers who thrilled to the dramatic plea—"Quick, nurse, the adrenalin!"

Harvard University scientists explained its role in the living body and proved it was the "emergency stimulant"—the substance that quickly mobilizes every bodily organ for fight or flight.

A pair of English researchers (with the aid of a professor of dead languages) gave to adrenalin and all similar chemicals the name *hormone*, a word which any good Greek could translate into *I arouse*. Hormones, it appeared, were arousers and stimulants of the first order. Adrenalin was the first hormone to be obtained in the form of a pure chemical.

Three years after the Abel-Takamine difficulty, adrenalin also became the first hormone to be obtained by artificial creation in a test tube. In 1903, chemist Friedrich Stolz, working secretly in a German industrial laboratory, barely nosed out his competitors by synthesizing adrenalin from a coal-tar by-product. His synthetic compound cost only about half as much as the natural hormone extracted from the glands of animals in Chicago slaughterhouses.

III

In 1856, Moritz Schiff of Frankfort found dogs and guinea pigs would die if their thyroid glands were snipped out. Later he made the remarkable discovery that he could save his animals by taking those cut-out thyroids and planting them almost anywhere under the skin. It was eloquent proof the thyroid was vital to life, but who cared?

It was pointed out to good Dr. Schiff that everybody was born with a thyroid gland, everybody kept his thyroid gland, and nobody ever lost a thyroid gland. There was not the least reason to get excited. Why, you might as well waste time by proving the head is vital to life, too!

But there was reason enough to get excited. There were babies who were born with thyroid glands, true enough, but some of them had thyroids which were lazy. There were glands up in their necks, but the glands weren't working. And these victims were horribly misshapen, drooling little beings with protruding tongues and abdomens; they grew up (sometimes!) to be stunted, bandy-legged, imbecilic dwarfs known as "cretins."

There were other victims, older ones, who also had thyroid glands—good glands, too, which kept on working smoothly for ten, twenty, thirty, forty years. And then, mysteriously, these folks slowly lost their vitality and enthusiasm. They became fat and flabby. Their skins dried, their memories failed, and they would have been much better off dead.

And finally, thanks to surgery, still a third group appeared on the scene. In the early 1870's, a school of skillful Swiss surgeons began to treat goiter by cutting out the thyroid gland. Their patients got over their goiters, all right, but very soon they became weak and listless, fat, dry-skinned, weak-minded, and stupid.

Back into the picture strode Moritz Schiff. "Those surgeons are crazy!" he thundered. "They're wrecking people by cutting out the thyroids. If dogs can't live without thyroids, then neither can human beings. . . ."

Twenty-five years before, he had been convinced of that, and now he was surer than ever of it. But why was the thyroid so vitally necessary? What did it do that was so essential for health?

Well, it certainly didn't do anything that could be done only in the neck, for he had already proved the gland could be transplanted elsewhere and all would still be well. Apparently the thyroid would do the job it was supposed to do, just like a factory, no matter where it was located. Probably it took in raw materials, just like a factory, and turned them into a product which was poured into the blood. . . .

Could some of that product be found in the thyroid gland itself —in a piece of raw thyroid carved out of a dog or a sheep or a cow? He took fresh thyroid tissue from a slaughtered animal and fed it to patients who had undergone goiter operations. He took thyroid juice and injected it under their skins, into their veins.

What happened? For twenty-four, forty-eight hours, nothing. And then on the third or fourth day, his patients lost their deadly indolence and weakness, and their minds began to come awake. It was a miracle, but a brief one; for after a few days, the patients slowly sank back into their lethargy. Yet—and Dr. Schiff gloated as he reported it—he could keep giving them thyroid every day and keep them alive and healthy and sane.

Could the surgeons cure goiter with an operation? Splendid! But he, Moritz Schiff, could cure the cure with thyroid juice!

Quickly other doctors pounced on his report. "If Schiff's treatment will work for patients who have had their thyroids cut out," they dreamed, "then maybe it will work on those whose thyroids are in place but not active."

So these dreamers took cretins and began to cure them with thyroid juice and thyroid pills. They took other patients who were overweight, tired, dry-skinned, mentally exhausted; and these, too, they cured. They cured them once, with one treatment, and they kept them cured by continuing the treatments for months and months, for years and years.

The pride of the British medical profession was one old lady

who was kept alive and well for twenty-eight years, until she died at the revered and logical age of seventy-four. It had taken the juice from the glands of eight hundred and seventy sheep to chalk up that record, but there were plenty of sheep. . . .

Abel and Takamine had found the juice of adrenal glands was potent because that juice contained a superpotent chemical. What was in the juice from the thyroid glands?

In 1910 a twenty-four-year-old biochemist in Detroit started on the track of the thyroid chemical. A year later he moved to Saint Luke's Hospital in New York and kept on with the search. In 1914 he went to the Mayo Institute, and by then he knew he was getting close.

Young Edward Kendall knew the thyroid chemical contained iodine; he had checked the activity of each extract by testing its effect on dogs and sick children and also by measuring its iodine content. In November of 1914 he told his Mayo colleagues he had a portion containing 26 per cent iodine—then another with 35 per cent, then 42 per cent, then 47 per cent. The higher the iodine, the more powerfully it worked on dogs and children. And then, "Can't seem to do any better," he wailed, "and I still haven't got what I'm looking for!"

It was December of 1914, and Dr. Kendall started to write a scientific report on his work, a report to be read at the forthcoming meeting of the Federation of American Scientific Societies at Saint Louis.

The days flew by; the report was nearly complete; but the laboratory experiments were still getting nowhere. On December 24, with the report all nicely polished and typed, there was just time for one more experiment before Kendall had to leave for Saint Louis—an experiment which he wrecked. "Damn!" he muttered. "Heated it too long. Well, maybe I can still save some. . . ." He mixed up the dirty residue with a little alcohol and alkali, then added some acetic acid and went home. It was Christmas Eve.

The next morning—only a crazy scientist works on Christmas morning—Kendall shivered his way through the icy streets, walked

into his laboratory, looked at his solution. There, along the edges, he spotted bunches of needlelike white crystals. Crystals!

He rushed to do an iodine analysis, and then—60 per cent iodine, the highest he'd ever had.

"Well!" he breathed. "Well! Well, merry Christmas!"

Three days later, on December 28, he reported his findings to all the scientists at Saint Louis. "I don't know what the crystals are or what they do. . . . I'll have to tell you about that later."

Back he went to the Mayo laboratories and started to make more of this stuff. After all, this first accidental experiment had yielded only fifty milligrams, one six-hundredth of an ounce, of his mysterious crystals. Hardly enough for animal tests! He started all over again with more thyroid glands, and this time he prepared two hundred milligrams of it. Some of this was injected into dogs, some into a misshapen, imbecilic little cretin, and some into a patient suffering from the first signs of a lazy thyroid.

"The administration of the compound," he reported, "was promptly followed by relief of all signs of thyroid deficiency."

And there it was, as dull, as unexciting, as commonplace an announcement as could be written. But it told the story. His compound, his Christmas present from the frittered experiment, was the chemical he wanted—the active ingredient of the thyroid gland. It was named *thyroxin.*

Now the Mayo laboratory underwent a nightmarish change. In place of shiny glassware, there appeared galvanized iron tanks and huge enamel kettles. In glassware, Kendall could make only milligrams of his chemical, and he needed pounds of it. It was a tough job, much tougher than he anticipated. From three and a half *tons* of fresh hog thyroid glands, he isolated a little more than one *ounce* of thyroxin—and that took him five years!

One commercial outfit offered to put this ultrapure thyroxin on the market, but the wholesale price of about ten thousand dollars an ounce didn't attract many customers. Most doctors preferred a slightly purified but very cheap thyroid extract to use on their patients.

Meanwhile a young English student, Charles Robert Harington, started a different approach to thyroxin. He didn't want to isolate thyroxin; he wanted to synthesize it. That took two years of heart-rending work, plus a dozen hunches that seemed too perfect to be scientific. But the work and the hunches and the help of smart Professor George Barger at Edinburgh brought success, and young Harington found how to make synthetic thyroxin. Just like Kendall's product, this synthetic hormone would do everything the whole thyroid gland could—and would do it in a quite amazing way. The most infinitesimal amounts would help the body—less than a hundred-thousandth of an ounce per day!

English scientists, looking very definitely at America and at Germany, commented pointedly that young Harington did not patent his discovery.

IV

An old Greek physician once penned a horrifying and yet reasonably graphic description of diabetes. "Diabetes consists of a moist and cold wasting of the flesh and limbs into urine," he wrote. "The patients never cease making water, for the discharge is as incessant as a sluice let off."

It wasn't an encouraging description, but then there wasn't anything encouraging about diabetes. Its cause was wrapped deep in terrifying mystery, its cure unknown. That was true ten thousand years ago, and it was true in the nineteenth century—up to 1889.

In 1889, the very year Brown-Séquard launched hormone science, two workers in Germany and a third in Italy were starting off on a remarkable new track. At the University of Strasbourg one morning, Professor Bernhard Naunyn outlined a proposed experiment to two of his assistants. "Gentlemen," he said, "it might be interesting to learn exactly how important the pancreas is—to find if it's really necessary for life. Suppose you remove the pancreas from an animal and see what happens."

Josef von Mering (who later would help discover veronal) and Oscar Minkowski went to work. On a balmy June day, they took a nice little lady dog, knocked her out with a few whiffs of chloroform, and then very carefully cut a long slit in her abdomen. Through this incision they reached down by the stomach and grabbed the elongated flap of an organ known as the pancreas. With sterilized scissors they cut off three-quarters of the pancreas and then sewed up the wound.

Within a few days, they had answered part of their question: the dog certainly didn't need all her pancreas. Although three-quarters of it were sitting in a jar of alcohol on a laboratory shelf, she was getting along beautifully.

Three weeks later, the two German doctors again opened their dog's belly, and this time they cut out every last remaining bit of the pancreas. On the next morning, their animal was very, very sick. She was lying around weak and helpless, struggling to her feet only to urinate—a painful act that took place with surprising frequency.

And then a laboratory assistant called von Mering's attention to that urine, for it was attracting swarms of flies. A quick test showed it was loaded with sugar!

In another three weeks, the dog was dead. She had been growing steadily weaker, and an attack of pneumonia put her out of her misery. But these Germans were smart enough to realize the pneumonia had been only the final blow—the cause of the weakness, the sickness, the sugar in the urine, was something else. *It was diabetes.*

They published a splendid report of their discovery and announced that surgical removal of the pancreas produced diabetes in a dog. Perhaps, they ventured, the pancreas had something to do with diabetes in man. But what?

Now this was only one experiment, and sometimes a single experiment doesn't mean very much. But Dr. de Dominicis in Italy did the same thing and got the same result. Soon other doctors

tried that easy experiment, that deadly operation; and they, too, got diabetes in their animals. Dogs, rabbits, rats, guinea pigs—they all worked the same way.

But why? What did the pancreas, that organ every butcher knew as "sweetbreads," what did it have to do with causing—or perhaps preventing—diabetes?

Minkowski, one of the original pair who found diabetes came when the pancreas went, tried to do something about it. He took some pancreas tissue, squeezed it, pressed out a juice, and injected it into a dog which had no pancreas and was dying. The dog died. Minkowski gave up the problem in disgust.

Fortunately, other workers were getting quite excited about this pancreas-gland puzzle and were not giving up. American doctors, working in the Johns Hopkins dissecting rooms, looked very carefully at the pancreas glands of men who had died of diabetes, and there they found tiny signs of damage, of destroyed cells. Certainly, they said, there *must* be some connection. And more and more workers, thinking of Abel and his adrenal juice and of the thyroid workers and their extracts, tried to wring some life-saving juice from the pancreas.

Dr. Georg Zuelzer almost got it. Working at Berlin's Institute of Pathology, he found a pancreas juice that seemed to help his operated dogs, that even seemed to help eight human diabetics. But the patients cried and complained, "Herr Doctor, the injections make us feel sick and feverish. Look, there are sores where you put the medicine in. It hurts. . . ." And so Georg Zuelzer lost his enthusiasm.

An Italian veterinary expert, Dr. Massaglia, worked out an ingenious theory. "The diabetes," he explained, "is caused by laziness of certain tissues within the pancreas. These tissues are the 'islands of Langerhans' and normally control the use of sugar by the body." Then he went on to prepare an extract of the pancreas, but it didn't work.

In the United States, young Dr. John Murlin of the University of Rochester was hot on the track of a potent antidiabetes extract.

So were Ernest Scott and Professor Anton Carlson at the University of Chicago. By 1916 they were all getting close. Then America went to war, and her scientists turned to matters more important than a cure for diabetes.

By 1916, however, there were so many workers so close to an answer that the experts all agreed that within the pancreas—within the "island" or "insular" cells of the pancreas—there must be something which could lick diabetes. So convinced was Professor Schaefer, the Englishman who helped track down adrenalin, that he proposed a new name for it:

"If this hypothetical substance is isolated," he suggested, "it might well be called *insulin*. . . ."

Back from the war in 1919 came twenty-seven-year-old Frederick Grant Banting, nicely equipped with a Military Cross and the scar from a Cambrai wound. Fred Banting didn't know much about diabetes: he was a surgeon—without a job.

He came back to his native Canada, got a residency at the Hospital for Sick Children at Toronto, and then was appointed assistant in physiology at Western University in Ontario. He didn't know too much about physiology, either; he had to work hard studying late each night to prepare lecture notes for the next morning in order to keep ahead of his students. On the night of October 30, 1920, he was preparing the notes for a lecture on diabetes.

He had been reading in his little room for hours, going over textbooks and journals, and finally picked up a copy of the latest issue of *Surgery, Gynecology and Obstetrics*. He turned to a paper on the pancreas by Professor Moses Baron of Minneapolis. It was late, way after midnight, and his eyes were red and tired . . . and who was Baron, what did *he* know?

Suddenly Fred Banting came wide awake—this fellow Baron knew plenty! There is a duct leading from the pancreas to the intestines. If this duct is tied off so nothing can pass through it, then strange things begin to happen in the pancreas. As a result of this

stagnation and backwash, Baron had found, certain parts of the pancreas are destroyed.

These parts are the regions where trypsin is located—*and trypsin is the stuff that can destroy insulin!*

All at once, Banting had worked out a wonderful theory, complete in virtually every detail. The pancreas, as everyone knew, contained two powerful substances—insulin (which nobody had yet actually found) and trypsin. When the pancreas is in the body, everything remains friendly between these two. But when the pancreas is removed from the body, trypsin declares war on insulin and destroys it.

That was why pancreatic juice, prepared to combat diabetes, was no good—*because while it was being prepared, the trypsin had destroyed every bit of insulin!*

And now Professor Baron, down at Minneapolis, had shown how the trypsin could be removed. . . .

Banting reached for his notebook and a pencil—"Tie off the pancreatic ducts of dogs. Wait 6–8 weeks for degeneration. Remove the residue, and extract."

There, in three brief sentences, was the answer to diabetes.

A few weeks later, Dr. Banting stood in the office of the eminent Professor J. J. R. Macleod at the University of Toronto. Time after time, Macleod had been pestered by bright young scientists who were convinced they had the solution to something or other. Now he listened to Banting's solution to diabetes. It sounded no more practical than a hundred other theories. But Banting wanted so little.

"Now, just what do you need?" asked Macleod.

"The facilities of a small laboratory, an assistant for eight weeks, and ten dogs."

Macleod peered at the young surgeon. "Very well," he decided, "you shall have them."

And then Macleod offered one thing more, a bit of advice that was going to mean the difference between success and failure. "In

testing your results, Dr. Banting," he suggested, "don't try to judge whether your animals *look* better. Don't even try to measure the gas they inhale and exhale—that's too difficult. But you might measure *the amount of sugar in their blood. . . .*"

In the spring of 1921, Banting got his little laboratory, his ten dogs, and his assistant—Charlie Best, who had just finished his first year in medical school. Young Best didn't know anything about diabetes, either, but he could measure sugar in blood, which Dr. Banting thought was amazing. Banting couldn't measure sugar, but he was a surgical wizard. He took healthy dogs, just as he'd planned, and tied tight knots of thread around their pancreatic ducts. He waited for nearly two months until the trypsin had time to degenerate. Then he cut out the pancreas.

That piece of tissue was chopped, macerated, squeezed, and a few drops of juice were caught in a vial. That juice—if his idea were right—that juice should cure diabetes.

By midsummer, the two young men were all set to find out. Their laboratory was ready, their sugar-measuring solutions were bottled, their glassware was clean, their operating bench in place. In the middle of July, they started on the first experimental dog, cutting out first only part of the pancreas and then all of it. On July 30, they had a dying dog.

They strapped that poor beast on a table, and then Banting exposed a vein in its leg. He punched into it with the needle of an empty hypodermic syringe and drew out a little blood. "Here, Charlie," he said, "let's see what the sugar is first."

In a few minutes Charlie Best straightened up from his desk. "It's about two hundred," he reported. "He's loaded with sugar."

Normal sugar, for a healthy dog, should have been one hundred and twenty.

Then Banting picked up another hypodermic and injected forty drops of the precious pancreatic juice—juice from which all the trypsin had been removed. He shoved that juice into the dog's vein and then sat down to wait for sixty long, dreadful minutes. Then he looked at his watch.

"Eleven o'clock. Let's take another sample."

He drew out another blood sample and handed it to Best; young Best started the second analysis. In a few moments—ages to both of them—he had his answer.

"What is it?"

"It's down, Fred!"

Banting wiped a pint of sweat from his face. "How much?"

"Down to one hundred and twenty," Best answered. "It's normal!"

They had performed a miracle, and they both knew it. They had taken a diabetic dog, its blood sweet with sugar, and pushed it down to normal. They had saved the dog's life—for a few days. Certainly their insulin—for that's what they'd found—would save a dog's life, but they didn't have enough insulin to make their miracle practical.

After all, a diabetic dog—or a diabetic man—needed a couple of insulin injections every day. And Banting and Best could extract only a tiny bit of insulin, enough for one or two injections, from one animal. Good Lord, they couldn't sacrifice two dogs a day to save even one human life—there weren't that many dogs!

That was the summer of 1921. By autumn they were still going, seeking a better way to get insulin. The original grant of eight weeks had long since expired, and Banting had been spending his own and Best's money to buy dogs and supplies; they were both nearly broke.

Soon Banting hit on a new way to get larger supplies of insulin. Other workers had already found that the pancreas in unborn animals held plenty of active insulin and no insulin-destroying chemicals. He began to get insulin supplies from the stockyards, where there were plenty of unborn animals in the wombs of slaughtered cows.

In Christmas week, seven months after they'd started their research, the Canadians went to Yale University and made their first report before the American Physiological Society, a report

only on animal experiments. They returned to Toronto and started on their first human patient.

In the Toronto General Hospital lay fourteen-year-old "L. T." He had started on the sugary path to death two years before. Now he was pale, terribly underweight, his hair falling out, mentally dull; there was sugar in his urine, and his breath had the deadly "diabetic taint."

The doctors had lost all hope. "He's practically gone," they said. "Give him a few weeks, maybe a few months, but it's hopeless."

So they selected L. T. for their first trial patient. They started him on insulin on January 11, 1922.

Within three weeks, every doctor on the ward was willing to certify that L. T. had been yanked from the grave. He looked and felt better, more active, brighter, stronger. Sugar no longer flooded his blood stream and spilled out in his urine. His urinalysis went from the deadly 4-plus down to 2-plus, 1-plus, and then to 0.

Was it actually the insulin that had worked this wonder? For two weeks, injections were stopped, and L. T. began to slip again. The sugar count went up to 2-plus, up to 3-plus. Then the injections were started once more, and the boy climbed back quickly to buoyant, amazing health.

The injections, however, were no easy boon. There was more than insulin in that pancreatic juice, and some of those extra chemicals were hellishly painful—there was too much screaming and writhing and agonized cries. Then Professor Macleod, that remarkable—and very jealous—man who always hovered in the background, brought in Bert Collip from Alberta. Collip was a brilliant chemist who stepped into the mess, learned how to purify insulin, and prepared a safe, painless product. Without his help, insulin would have been a very mixed blessing.

Now the Canadians had precious little time to make reports; they were too busy trying to acknowledge a flood of congratulations, a swarm of medals and awards, appointments to lofty positions, and finally the Nobel prize.

The Nobel award went officially to Banting and Macleod. Banting promptly split his share with Best, and Macleod divided his with Collip.

For one time in history, there was enough honor to go around.

V

By now it was 1924, and the hormone-hunters were getting the feel of their jobs and becoming so proficient it was impossible for any one man to dominate the field; instead of a single important discovery reported every few years, the announcements came out in a steady stream.

John Jacob Abel, the man who had nearly discovered adrenalin, went ahead with insulin to isolate pure crystals of the hormone.

J. B. Collip, who had won his laurels in the insulin hunt, and Adolf Hanson, a country doctor in Minnesota, found *parathormone* in the parathyroid gland to prevent convulsions and protect bones.

Three groups of Americans working at Buffalo, Cleveland, and Princeton isolated a whole batch of hormones known collectively as *cortin*. It is cortin which guards against Addison's disease, the fatal ailment marked by bronzed skin and overwhelming weakness.

Meanwhile, another group had gone probing into the most fantastic gland of all, the pituitary. Located deep within a fold of the brain and weighing about as much as a split pea, this tiny organ was exposed as the master gland of the entire body.

Drs. Herbert Evans and Joseph Long at the University of California were aware as early as 1920 that there was something peculiar about the pituitary. Other workers had already discovered that removal of the gland, an exquisitely delicate operation in itself, resulted in a series of unpleasant changes in experimental animals, but no one knew exactly what had happened.

The Californians arranged with near-by slaughterhouses to get the pituitaries from cattle a few hours after the animals were killed. From the front section of these glands, the scientists prepared an

extract and fed it to dozens of rats. The animals digested this extract and showed no results, good or bad. The scientists increased the dosage and tried again, and still the rats remained unconcerned. Even when the animals were given "massive" mouthfuls of the stuff, nothing happened.

"If there is anything in the pituitary that affects the body," thought the scientists, "it certainly doesn't work by mouth. Maybe it might work if we inject it under the skin."

They changed their procedure and began shooting this extract into a new batch of young rats scarcely two weeks old, and then they got action. A baby rat grows pretty fast under any conditions, but Evans and Long had never seen animals grow as rapidly as did theirs. Day by day, the injected rats put on an amazing amount of weight, far exceeding their untreated brothers and sisters.

At the end of the experiment, the pituitary-treated animals were literally giants, twice as heavy as the largest rats ever seen in the laboratory. And that extra weight wasn't merely fat—it was distributed in bigger and longer bones, larger and heavier organs. In addition, the treatment apparently did odd things to the sex organs.

Their report, showing the pituitary was certainly involved in regulating body size and perhaps in controlling sex development, sent a whole army of scientists to work. Drs. Philip Smith and Earl Engle at Stanford University picked up the trail at once and proved beyond doubt that the pituitary is the gland which bosses sexual maturity. If the pituitary is in place and functioning like a good little gland, the animal matures sexually in the normal time. If the pituitary is cut out, sexual maturity is delayed or prevented completely. But even if the gland is removed, sexual maturity may still be produced by injecting the animal with an extract of pituitary substance.

While these Stanford workers were rounding up their findings, a pair of Germans were confirming that discovery and extending its application in a surprising direction.

"This sex-stimulating stuff in the pituitary is undoubtedly a hormone," said Dr. Bernhard Zondek. "If that is so, it must be pro-

duced in the pituitary and then spread around the body in the blood stream. It is undoubtedly also flushed out of the blood through the kidneys and is present in the urine."

"Do you mean we should look for it there?" asked Dr. Selmar Aschheim. "But how could we detect it?"

"Merely by concentrating the urine, injecting it into immature animals, and seeing if the injections produce sexual maturity."

"But where will we get the material?" asked Aschheim.

"That is my affair." So Bernhard Zondek, who was one of Berlin's bright young specialists in women's diseases, ordered urine samples collected from all his patients. He had the material properly treated and then injected it into baby animals.

For weeks, the two doctors performed their tests—injecting material into their animals, waiting a few days, sacrificing the animals, and then examining their sex glands.

"Here's one," said Aschheim, "and it's certainly become mature. Its ovaries are beautifully developed."

"Good," said Zondek. "Where did that urine sample come from?"

"From Frau Obermeyer," answered an assistant. "She is in the hospital to have her baby."

"Here's another," said Aschheim, "and it's mature, too."

"Excellent," remarked Zondek. "Who was the patient?"

"That sample came from Frau Richter. Another pregnancy case."

"Wait, here are two animals that didn't mature at all," said Aschheim.

"Damn!" snapped Zondek. "Where did those samples come from?"

"One is from Frau Horst, who has cancer of the womb, and the other comes from Fraulein Mannheim. She has infected tubes."

Zondek held up his hand. "Wait a minute. In two cases, the urine from pregnant women produces sexual maturity in our animals. In two cases, the urine from nonpregnant women has no effect. I think we have here a laboratory test for pregnancy."

"What!" said Aschheim. "But we have done only four tests. Four tests do not mean anything. It is just a coincidence."

Zondek shook his head. "It is no coincidence. Go ahead, try some more tests. You will see I am right."

More tests were made. Zondek rounded up all his patients and all the patients he could get from other Berlin gynecologists and obstetricians. Aschheim performed hundreds of autopsies on his little animals, peered at their ovaries for signs of maturity, and filled page after page with his notes.

Each time the injection produced maturity in those animal ovaries, a check on the records showed the sample had come from an expectant mother. Each time the injection was ineffective, the records showed the woman was not pregnant.

Now Zondek began looking for women who might be in the earliest stages of pregnancy, and soon he told these astonished mothers-to-be that the laboratory had disclosed their deepest secret.

"Whether you know it yourself or not," he would announce, "you are definitely pregnant."

"It is impossible," many women would retort indignantly. "After all, there are some things we know better than you."

But within a few weeks they would have to admit that Dr. Zondek had been right.

The world soon heard of the marvels of the new Aschheim-Zondek pregnancy test, and even doctors were amazed that an injection of concentrated urine into baby animals would quickly reveal secrets which formerly would remain hidden for several months.

At first Aschheim and Zondek thought their test was based on a hormone which had passed from the pituitary gland out through the kidneys; only after many months of work did they discover the hormone involved was actually produced by the placenta around the growing embryo. No wonder then that the test was positive during pregnancy!

This discovery, which had actually started from an investigation on the pituitary, sent still more researchers after the mysteries of that little gland. They learned that the pituitary plays dictator to

all the other organs. It tells the body to be a giant or a dwarf. It tells the thyroid gland when to work. It runs the adrenal glands. It controls the pancreas. It tells the sex glands when and how to grow; it governs pregnancy, delivery, and milk-secretion. It controls muscle contraction and blood pressure. It is very definitely the boss, and its official notices are sent out in the form of hormones.

The powers of this tiny organ were breathtaking, but not so startling as some of the hormones extracted from still other glands. These were the male and female hormones, the chemical causes of sex.

Under the brilliant leadership of Drs. Edward Doisy and Edgar Allen of Washington University in Saint Louis and young Dr. Adolf Butenandt in Berlin, the hormone-hunters turned up three potent chemicals responsible for femaleness. These substances, *estrone, estriol,* and particularly *estradiol,* were tracked down first to the ovary, where they might well be expected to occur, and then they were found in the most surprising places—in female willow flowers, palm kernels, and, most surprising of all, in the urine of stallions, male zebras, and male donkeys!

These female chemicals could be injected into castrated animals and would stimulate the mating instinct, the formation of female hair-distribution or plumage, the female voice, and the female breast and hip development. And these compounds were almost unbelievably powerful—one ounce of estradiol was enough to produce estrus (the mating reaction) in eight hundred and fifty million female mice!

In practical medicine, they could be used to treat women whose ovaries were destroyed or removed, whose natural supply of female hormones was too low, or whose whole nature was thrown out of adjustment by a sudden "change of life" and who might be heading for the divorce court or an overdose of sleeping powders.

Physicians could also use a second type of female hormone on their patients. This was *progesterone,* which stops menstruation, helps the embryo hang on, and keeps the womb quiet for nine months. Although the body produces progesterone in large quan-

tities during pregnancy, chemists can make it artificially even more abundantly and less expensively from soybeans. This synthetic hormone has proven invaluable in preventing many spontaneous abortions in pregnant women, and in relieving undue menstrual pain in nonpregnant women.

Still a third type was uncovered by chemists working in a veterinary laboratory. This *equine gonadotropin,* found in the blood of pregnant mares, stimulates the ovaries to go to work.

Almost all of these female hormones have been isolated in pure form, crystallized, their formulas determined, and finally prepared in a test tube.

All these discoveries helped to explain why women (and a few unfortunate men) are women. For the males, scientists started with a clue turned up at the University of Chicago. In the laboratory of Professor Fred Koch, twenty-five-year-old Lemuel McGee wrote his thesis to win a Ph.D. degree and in it announced the isolation of an extract from bull testes which could produce all the male characteristics just as estrone produces the female characteristics.

Four years elapsed before McGee's findings took the next step forward, and then, in 1931, Butenandt announced he had isolated a male hormone, *androsterone,* in pure form—three-hundredths of an ounce from twenty-six thousand quarts of raw material! Three years later, Dr. Leopold Ruzicka in Switzerland created it synthetically from the grease of sheep's wool.

It soon seemed likely, however, that another male hormone must exist, for androsterone was entirely too mild and weak to produce much effect. In June of 1934, Dr. Ernest Laqueur in Amsterdam isolated crystals of a new hormone from the sex glands of bulls, named it *testosterone,* and proved its high potency. This, he announced, was the real male hormone.

Now testosterone was dreadfully expensive to isolate in its natural form. If it could be manufactured synthetically, it had a potential million-dollar market for the treatment of male sterility, impotence, and the unpleasant senility of old men. It could do almost all the things that old Brown-Séquard had looked for.

Furthermore, there was a rumor in high scientific circles that the Nobel prize committee was getting ready to make an award for hormone work—Butenandt was already slated to receive half the award (he couldn't accept it anyhow, due to the Nazi ban), and the committee was looking for a running mate. A flock of scientists started on a race to synthesize testosterone.

A month, two months passed after Laqueur's announcement, and nobody claimed the discovery. Testosterone was a tough chemical to crack. . . .

In Zurich, Professor Leopold Ruzicka said farewell to his colleagues at the Technische Hochschule. "Keep working on that testosterone," he directed. "If I get any ideas, I'll let you know." Then he left for the United States, where he was to give a series of scientific lectures.

All the way across the Atlantic, the Swiss scientist wondered about the testosterone formula. He worried and fretted and drew countless diagrams on countless scraps of paper, but no brilliant idea would come. He reached New York, talked to a few people, and then—bang!— the solution came to him. Now he knew how that testosterone molecule was put together! He rushed off a cable to Switzerland and climbed on a train to San Francisco.

At San Francisco, chemists from all over the country had gathered for the convention of the American Chemical Society and to hear the famous Professor Ruzicka give his talk on hormones. Before the convention opened, a newspaperman knocked on Ruzicka's hotel-room door.

The door opened and the scientist peered out. "Yes?"

"Dr. Ruzicka," said the reporter, "I'd like to have an interview. Could you tell me what you're going to say in your lecture?"

"Ah, please." The distinguished chemist bowed deeply. "Can you come back tomorrow?"

On the next day, the little ceremony was repeated. "I am so troubled," said Ruzicka. "I have not yet decided what I am to say in my lecture. Can you please come again tomorrow?"

On the third day, the reporter tried again. He knocked at the

door, and out bobbed Ruzicka's round, smiling face. "Ah," said the professor, "my friend from the newspaper. Come in, come in. I have a very nice little story for you today. I let you announce in your newspaper, for the first time, the discovery of the synthetic male sex hormone—synthetic testosterone. It was," he fondled a cablegram tenderly, "it was synthesized by me in my laboratory in Zurich. . . ."

The cablegram slipped to the floor. On it the reporter spotted one word: SUCCESS!

CHAPTER X

The Red Assassin

DOMAGK AND THE SULFA-DRUGS

FATE with an outrageous sense of humor arranged the tale of the red assassin—a story built of brilliant genius and intense rivalry, a story complete with mystery and war and dollars and death.

Fate saw to it that a sad-faced little pathologist became a hero in the eyes of the world, while behind the scenes two master-chemists fought and pulled and manipulated for the sheer pleasure of it. This was an epic of science, but much more it was a story of men.

It was this fate, then, that, during Easter of 1908, brought the Association of German Chemists to meet in the old city of Jena. That year, the president of the association was Carl Duisberg of the Bayer Works, who was consumed with a burning ambition to unite all Germany's chemical industry into one mighty unit. One day during the convention, Duisberg slipped away from the meeting hall to visit his old friend Ludwig Knorr, professor of chemistry at the University.

"Professor Knorr," said Duisberg, "it happens I have an opening in my organization for a very superior young man—someone who is well trained, careful, who has imagination. Is there anyone whom you could recommend?"

"Is there? Ah, there is, indeed," beamed Knorr. "I have the very man for you, my assistant, Dr. Hoerlein. He has worked with me for years. Done most of our studies on morphine. His chemistry is perfect, and you'll find he . . . well, he is no ordinary chemist.

He has studied politics, finance, business. He knows the role Germany can play in the world."

So Heinrich Hoerlein, who knew more than chemistry, went to work at the great Bayer plant.

"I leave to you the choice of your researches," Duisberg told him. "If you prefer, you may continue with your morphine studies. You can work on aspirin derivatives. You might be interested in explosives, or dyestuffs, or fertilizers. Anything you like."

Hoerlein said, "I think I should like to start with dyestuffs."

"Excellent. Your desk will be ready for you in an hour."

Hoerlein was placed in the care of two experienced Bayer dye chemists. He began with a study of para-amino-benzene-sulfonamide, a new dye-intermediate just discovered by some youngster in Vienna, a compound that formed dyes that were amazingly waterproof, that clung firmly to wool fibers. From it, he compounded supramin-red, walk-orange, supramin-yellow, and a whole assemblage of brilliantly colored chemicals.

Six months later, he requested a change. "With your permission," he told Duisberg, "I should now like to transfer to the drug department."

"Certainly," said Duisberg, "the change will be made immediately. Keep up your good work."

Hoerlein became a member of the pharmaceutical department, then its head, and finally a member of the board of directors. By now, Duisberg's dream had come true, and the Bayer Works had become part of the tremendous I. G.—the I. G. Farbenindustrie. The medical division of this great dye-trust was placed in Hoerlein's hands and grew so complicated that eventually he needed help to run it. He selected one Gerhard Domagk to direct the I. G.'s Institute of Experimental Pathology.

Here, then, were two of the actors in this story of the red assassin—Domagk, the official hero, and Hoerlein, one of the master-chemists who pulled the wires. At this very moment the other master-chemist, Ernest Fourneau, was busy in the Pasteur In-

stitute at Paris, trying to slaughter trypanosomes with arsenic.

The play was ready to begin.

II

Gerhard Domagk had been born in 1895 in the little town of Lagow. At the end of the war he was only twenty-three and had already practiced medicine for three years—without benefit of any medical education. Discharged from the army in 1918, he entered medical school at the University of Kiel. He graduated, practiced for a few years, taught for a few, did research on cancer, and in 1927 went to work for Hoerlein at the I. G.

Now the I. G. was no university. It was definitely Big Business. Did Dr. Domagk wish to make experiments in pure science? Well, that could be done—after all, research in pure science brought prestige, but there were stockholders in the I. G., and they didn't want prestige nearly so much as they wanted dividends. Therefore, Dr. Domagk should keep his eyes open for any new chemicals which might cure disease, *particularly new chemicals which might be patented.*

They permitted Domagk to go ahead with his cancer studies, with his bright new stains to diagnose the disease, but they looked more kindly on his blundering attempts to find a cure—he tried hundreds of chemicals in such a rush that he failed to learn whether any one of them might be useful.

Domagk could also go ahead with his search for the cause of cirrhosis of the liver in rabbits. That was fascinating work and probably very important to rabbits. But much more interesting to his employers was this nice yellow chemical, trypaflavine, with which Domagk was supposed to save dogs from a very unpleasant malady.

It wasn't much fun for poor Domagk, pottering about to discover new drugs, when he'd much prefer to look down a high-powered microscope at sliced cancer tissues. "I don't know enough

about drugs," he argued to himself. "Why can't they let me do my own work?" But the I. G. was paying his salary; the I. G. wanted new drugs. . . .

In 1930, Hoerlein had a splendid idea and proceeded to saddle it on Domagk. "Why don't you go after some drug that will kill streptococci?" he asked. "There isn't anything today that can touch them. I'll have Klarer and Mietzsch prepare some new chemicals for you."

Streptococci? Domagk sniffed. Lovely microbes, those! Merely the evil germs that cause blood poisoning and childbed fever, scarlet fever and erysipelas, the germs that commit murder through an infected ear or toe, the very worst germs in the world, the "captains of the men of death."

"And I should discover something that will kill these strepts," Domagk murmured. "Oh, well. . . ."

There were plenty of things that *might* kill strepts. Dozens of old chemicals had been proposed, and now chemists Fritz Mietzsch and Joseph Klarer began preparing still newer ones. They created an entire family of compounds, rich in gold, that worked excellently in the test tube, even on infected mice, but were much too deadly for human beings.

They tried acridine compounds, but they wouldn't work even on mice.

They tried dye-chemicals, naturally, for the I. G. had plenty of them lying around; and these dyes looked rather promising, promising enough to keep Mietzsch, Klarer, and Domagk busy until they had studied hundreds of them.

One day in 1932, Domagk scurried into the office of Heinrich Hoerlein and laid a report on the desk. "Here, I think, is what we have been looking for."

"Ah," smiled Hoerlein, "so you found the strept cure. What is it?"

Domagk pointed to the paper. "Here is the formula."

Hoerlein looked, rubbed his eyes, looked again, and then scowled darkly at poor Domagk. "Where did you get this?"

"Mietzsch and Klarer made it. Why, sir, is anything wrong?"

"Of course not. Send Mietzsch and Klarer to me immediately. And Dr. Domagk, please do not mention this to anyone."

Domagk was ushered out.

For days, the bewildered scientist looked on as Hoerlein called conference after conference with his chemists, lawyers, and patent experts. There was shouting and table-pounding and careful planning behind closed doors. Secretaries and assistants, knowing something big was in the wind, exchanged bits of rumor, but nobody knew exactly what—nobody but Heinrich Hoerlein.

Soon there was more work to be done, more drugs to be tested against the strepts—drugs remarkably like the one Domagk had found to be so wonderful. Then more conferences and more lawyers, and finally on Christmas Day of 1932, Mietzsch and Klarer applied for a patent on a brand-new chemical.

It was a very ambiguous patent, merely mentioning the formula of the chemical and indicating it was a germ-killer. It looked just like the scores of other germ-killers which the I. G. discovered and patented each year—germ-killers which, if laid end to end, would have been a very good thing.

"You may go back to your cancer work now," Domagk was told. "We won't bother you any more with drugs. But please don't discuss that strept work, just forget it!"

So Domagk, delighted to forget about everything else and never suspecting his distasteful studies on strepts were about to win him a Nobel prize, went back to diagnosing cancer.

Heinrich Hoerlein possessed among his other titles an honorary professorship at the near-by medical school in Düsseldorf. He had good friends on the faculty there, and it was to one of them, kindly Hans Schreus, that the new drug was given for the first tests on human beings.

Dr. Schreus was a skin specialist, a man who might well need a good drug to combat the strepts. He put the chemical on his shelf and promised to use it at the first opportunity; perhaps on a

bad attack of erysipelas or a stubborn case of carbuncles. But the first case was neither of these.

One day he walked through the ward with his young assistant, Dr. Richard Foerster. They came to a bed and looked at a baby boy, only ten months old, red, feverish, and weak.

"How is the little one doing?" asked Schreus.

Foerster shrugged his shoulders. "Only a miracle can save him, Herr Professor. The skin infection has spread. The bacteria have now invaded his blood. This morning a blood culture was 2-plus. We've tried everything, but . . . well, tomorrow or the next day will probably be the end."

"Ah, that's too bad, Foerster, too bad. You say the bacteria are in the blood stream. What kind are they, streptococci?"

"No, Herr Professor, staphylococci."

"Staphylococci? Mm-mm, a pity. If they were only strepts, we might try something."

Foerster hesitated for a moment. "You have something new?" he asked. "After all, staphylococci are much like streptococci. Perhaps —perhaps this new treatment might also work on my patient."

"No," sighed Schreus, "that's impossible. But—well, what have we to lose? The child is dying anyhow. Come, Foerster, come with me to my office."

In his own room, Schreus pulled a bottle off his shelf, twirled it in his hands, watched the brick-red tablets tumble and roll.

"The I. G. says this is good for streptococcic infections. Here, take it and see what happens. Give the baby half a tablet now and another half tonight—if he's still alive. I'll stop in to see him later."

Half a tablet of the colored chemical, crushed in water, was forced down the baby's throat—carefully, very carefully, for the tiny patient was virtually unconscious.

In a couple of hours, young Foerster burst into his chief's office. "Professor Schreus, come quickly. Something terrible has happened!"

"For Heaven's sake, man, what? Is the child dead?"

"No, no, but his skin has turned bright red!"

"Oh," Schreus breathed, "you frightened the life out of me. That's all right, my boy. The drug I gave you is a dye. It's supposed to color the skin and the tissues. But, has anything else happened?"

"Not yet," Foerster answered. "The pulse is still weak. Temperature is about 104."

Another few hours passed, and the baby, now scarlet-skinned, lay gasping for breath. Its heartbeat was scarcely audible. The fever was still dangerously high. Time for another half tablet of the bright-colored drug, crushed in water. . . .

All that night, Foerster stayed in the ward—watching his little patient, feeling the child's pulse, taking his temperature. Early the next morning, he turned wearily around to find Schreus standing behind him.

"Herr Professor!"

"Good morning, Foerster. Well, how is he?"

"Herr Professor, I think the worst is over. The temperature is actually coming down!"

Three days later, thanks to a total of eight half-tablets of the red drug, Foerster admitted the baby was cured—cured of an incurable staphylococcus blood poisoning.

And cured by a drug recommended for another kind of bacteria!

"Astonishing!" exclaimed Foerster. "Remarkable!" agreed Professor Schreus. But that was only the beginning. This new drug was indeed the most astonishing, the most remarkable, the most unbelievable the world had ever seen. Domagk and his chemists had done their work well.

For months, only a few men in all the world knew this miracle had been performed. All through 1933, who knew that Domagk had found a miracle-drug? Well, there were Schreus and Foerster, of course; and, in Elberfeld, there was Otto Gruetz, who had cured an old lady with a deadly streptococcus rash. And in 1934, who knew about it? Hardly a dozen more doctors, who were testing it with phenomenal results on a few dozen patients.

And in 1933 and 1934, how many victims were massacred by

the deadly streptococcus microbes? There were at least a million and a half in Europe and the Americas alone—a million and a half men, women, and children who died from blood poisoning and childbed fever and all the other fatal strept diseases. They might well have used a potent strept-assassin!

Not until February of 1935—more than two years after the drug was discovered and patented—did the story break loose. Then, in the space of ten days, reports streamed from five great clinics.

Schreus of Düsseldorf announced the drug would cure erysipelas in two days. . . .

Gmelin of Essen reported curing blood poisoning in children. . . .

Veil of Jena claimed it would cure rheumatism. . . .

Anselm in the Jena women's clinic said it cured childbed fever. . . .

Klee and Roemer of Elberfeld announced it would cure infections from abortions, arthritis, kidney infections, tonsillitis, and "strept throat."

It would, indeed, cure almost anything. It was heralded as the greatest discovery since 606, since quinine, since the beginning of medicine. It was called *prontosil.*

And while these practicing physicians made their startling reports, all within ten days, Gerhard Domagk finally published his results—his experimental data to explain how prontosil worked.

"Prontosil doesn't work in the test tube," he said. "It only works in infected animals, but there it is remarkable. I took twenty-six mice and infected them all with lethal doses of streptococci. To twelve of them I gave prontosil. Of the fourteen animals that did not get prontosil, every one died. Of the twelve that did get the drug, every one lived."

It was a 100 per cent perfect experiment.

In France, in England, in America, scientists read that report and came upon that 100 per cent result.

"*Sacre!*" swore the French. "Does this Domagk think we are babes to believe such perfection?"

"My word!" exclaimed the English. "Isn't that just a bit thick?"

And in America, hard-boiled drug-testers looked at the results and said, "Oh, nuts!"

For there never was a drug that could give 100 per cent protection like that—complete protection against such a deadly microbe. Prontosil might save 80 per cent, perhaps 90, or even 95—and that would be sensational—but 100!

It was too pat, too ideal, too utterly perfect.

And come to think of it, why had the I. G. waited from Christmas of 1932 to February of 1935 to announce all these wonderful results?

"Ah," answered Heinrich Hoerlein, "that's very easy to explain. The results obtained with prontosil seemed too good to be true; so, before publishing them, several years were devoted to intensive clinical and experimental work."

Intensive clinical work? And yet in two years only a few dozen patients tested in all of Germany?

How strange!

III

Most of the French snorts and suspicions emanated from the Pasteur Institute in Paris, from the comfortable laboratories of Papa Ernest Fourneau. Papa Fourneau did not like Heinrich Hoerlein, and he did not like the great I. G., and he did not like Germany. And neither, for good and sufficient reasons, did Germany like Fourneau.

When Paul Ehrlich discovered arsphenamine, his 606 to battle syphilis germs, it was Fourneau and his Rumanian coworker, Constantin Levaditi, who introduced bismuth compounds to compete by doing the same job.

When Hoerlein's chemists brought out Bayer 205 to fight sleeping sickness (and perhaps to win back Germany's lost African colonies), it was Papa Fourneau with Levaditi and M. and Mme. Tréfouël who solved its secret formula.

Whenever the Germans came out with a wonderful new product, the French always did something to mar that triumph.

So Hoerlein did not like Fourneau, and Fourneau did not like Hoerlein, and now Hoerlein's boys had brought forth prontosil.

"Come, my friends," said Fourneau. "We go to work!"

They read all the reports by Domagk and by the doctors. They wrote to friends in Germany—for they still had a few there—and they compared notes.

"There is something here that does not meet the eye," Fourneau remarked. "Our good friend M. Hoerlein is playing games with us. He has found the most wonderful drug in the world. It cures everything. Yet, if he is so anxious to make money on his drug, why does he wait two years to place it on the market? To test it? Bah! The tests could have been finished in a month!

"And why does he let that silly Domagk publish those ridiculous 100 per cent experiments? Does he expect us to swallow such nonsense?

"And why do these very beautiful clinical reports contain so very few facts? Many nice adjectives, indeed, but not enough nice statistics.

"I think perhaps we should get some of M. Hoerlein's remarkable new prontosil and see for ourselves what it can do."

So Papa Fourneau and Levaditi and the two Tréfouëls went to work. In the first week of April, 1935, a letter went from the Pasteur Institute to the I. G., requesting a supply of prontosil "for experimental purposes." In reply, the I. G. stated it would be most happy to send this material, but first it would be desirable if I. G.'s Hoerlein and Pasteur's Fourneau might hold a little conference.

"Ah-ha!" commented Fourneau. "You see, this Hoerlein wishes to play games." And off he went to the conference.

It soon appeared these "games" were important, involving far more than a small supply of prontosil for experimental purposes. They involved big business, international business.

"The important question," said Hoerlein, "involves the sale of prontosil in France."

"Ah," said Fourneau.

"Now we understand we cannot protect prontosil in your country, since France does not allow medical preparations to be patented. That might work a great hardship on us."

"Indeed," said Fourneau. "A calamity."

"At any rate," the German chemist continued, "my company has been put to great expense in the development of prontosil. We have spent much time and much money. We have patented prontosil in Germany, in England, in America, and in most other countries. I wonder, therefore, if we might discuss the arrangements whereby prontosil could be sold in France. If these arrangements are satisfactory, perhaps we might make others of mutual satisfaction to France and Germany. . . ."

Fourneau shook his head sadly. "Alas, I am desolate. I can conceive of no such arrangements that would satisfy both your country and mine."

The conference was ended.

Back in his laboratory, Fourneau related the story to his associates. "I do not think we can count too heavily on M. Hoerlein's co-operation. Perhaps we may save time by making our own prontosil."

Soon the French chemists were busy synthesizing the red drug; since its formula had already been announced in official patents, there was little difficulty in making a good supply. At once Levaditi tested it on animals and found it to be astounding—almost as good as Domagk had claimed. Next, small samples were released to French doctors at the Claude Bernard Hospital, and these men, too, reported spectacular results on erysipelas and other streptococcus infections. And finally a French version of prontosil, competing directly with the drug manufactured by the I. G., appeared on the market. Hoerlein was greatly distressed.

"This is too much!" he cried. "These French have plagiarized a great German discovery. Their so-called scientists have robbed us with their imitation of our product. Germany's intellectual prop-

erty stands unprotected! It is all due to that despicable Versailles Treaty!"

There was certainly something to be said for Hoerlein's claims, but at the Pasteur Institute, he got little sympathy. "*Mon Dieu!*" remarked Papa Fourneau. "How that man talks!"

Meanwhile, he and his colleagues had begun to look suspiciously at the formula of prontosil, a most complicated formula, and they were wondering what made the red chemical such a splendid assassin of microbes. Chemist Jacques Tréfouël and his charming wife soon reported that the prontosil molecule seemed to be a lot more complicated than was actually necessary.

"Here is one-half of the molecule," they said, "merely a simple relative of aniline, plus sulphur and ammonia. It is interesting that if we tamper with this half, the product no longer kills germs. Undoubtedly this half of prontosil is important.

"But observe this other half. It is a complicated, color-producing coal-tar derivative. It is exceedingly interesting that we can change this part all we like, and the product still kills germs. Perhaps this complicated portion of prontosil is unimportant. Perhaps it is camouflage!"

So they cut off the suspected "camouflage," leaving the simple aniline derivative. It was so simple it could be made by any chemist in a jiffy. It was inexpensive. It was not red like prontosil, but perfectly colorless. And it was sheer murder for microbes!

They showed their results to Papa Fourneau. "Now we know why prontosil works," they announced. "It works because it contains this simple chemical."

"What simple chemical?"

"Why, this one—para-amino-benzene-sulfonamide. It, and it alone, is the streptococcus killer."

Fourneau beamed with delight. "Good! Admirable! It is a superb work you have made. Poor Hoerlein, we have done it to him again—now his wonderful prontosil patents are worthless. We can use this—this whatever-you-call-it instead, eh?"

"Indeed we can."

"But tell me something. This compound you have found—was it ever found before? Was it ever tested or used for anything? Was it ever patented?"

The Tréfouëls nodded. "It was discovered in 1908 and patented in 1909 as a dye intermediate. But that patent expired ten years ago."

"Ho-ho!" chortled Fourneau. "So the patent is no longer any good? Ah, tell me—who was the man who patented this chemical and never used it to kill germs, eh? Who was this poor excuse for a scientist?"

The Tréfouëls grinned. "It was an old friend of yours," they said. "It was Heinrich Hoerlein!"

IV

Here, then, was the explanation of the microbe-killing powers of prontosil. In the body, prontosil broke down to form para-amino-benzene-sulfonamide (a name soon shortened to *sulfanilamide*), and it was the latter which killed the germs.

And here, many scientists said, was the explanation of all the strange antics at the I. G. Now that these new facts had been divulged, these scientists concluded that Domagk must have "rediscovered" sulfanilamide—and that prontosil represented an attempt to hide sulfanilamide in a new, complicated, and patentable form.

Only Domagk or Hoerlein could cast light on this matter, but both men went around quietly with an air of outraged innocence. The Germans weren't talking.

Other and more important questions, however, were facing scientists. The problem of "who discovered what" could be argued indefinitely, but doctors wanted to know more about prontosil and sulfanilamide immediately. Which was better, and what diseases could they cure, and how should they be administered?

The Germans and the French had only partial answers ready,

and the English weren't too impressed by the claims of their continental colleagues. British medical authorities decided to make their own investigations. The honor of performing these first crucial tests was given to calm, reticent, distinguished Dr. Leonard Colebrook of Queen Charlotte's Hospital, just around the corner from Harley Street. Queen Charlotte's specialized in maternity cases, and Dr. Colebrook specialized in childbed fever.

Would Dr. Colebrook be willing to try prontosil and sulfanilamide against childbed fever? He would be delighted to cooperate.

Colebrook knew full well the treacherous foe he was facing. Every year, the Queen Charlotte's obstetricians tried to save about one hundred new mothers, women whose resistance was low, whose bleeding wombs had been invaded by virulent streptococci, and who might soon be faced with peritonitis or blood poisoning.

He knew that, of each hundred of these poor mothers, twenty-five would never live to see their babies. Could prontosil halt that terrifying murder? Could sulfanilamide?

Within a year, he had his amazing answer—using his drugs on sixty-four women dying with childbed fever, he saved sixty-one. He had cut the mortality to less than 5 per cent!

He had taken women who were inches away from septicemia or peritonitis or who had even entered these last, fatal stages—and he had saved them.

"The results," he said, "were quite striking."

Striking? If they hadn't come from Dr. Leonard Colebrook, no one would have believed them!

His first results were announced during the summer of 1936 when research men and physicians came to London for the International Congress of Microbiology. In his audience were men who had scoffed at Domagk and the Germans and who hadn't paid much attention to Fourneau and the French; but at the end of Colebrook's report, they were completely convinced. They stood in thronged corridors, in noisy hotel lobbies, in smoke-filled rooms, and marveled.

"Odd chap, that Colebrook," remarked one of them. "But the fellow does know his maternity business. If he says the bloody stuff works—well, I'm for it!"

"And I, too!" exclaimed another. "I come from Paris. I listen to my friend Fourneau, but I say to myself, 'This Fourneau, he is always too enthusiastic.' But now I am—how do you say?—sold. *Voilà!*"

"Sold? Oh, quite so," said the first. "You know, old Colebrook sold a lot of people this morning. Heard about one lad just a little while ago—he didn't even listen to Colebrook but got the report later—and he was so beastly excited that he sent cables back home."

"Cables? But why so much hurry?"

"Oh, this lad was an American, and you know how upset they get. He's from Johns Hopkins, I think. Name's Perrin Long. . . ."

Young Dr. Long of Johns Hopkins had been considerably excited. He had battled the strepts for years and had a husky respect for their devilishness. Now he heard these germs could be stopped by a couple of new drugs, and he wanted to see for himself. The cables and letters he rushed back to Baltimore were to set the stage for an experiment of his own.

That experiment started on the first day of September, and the first patients were mice—mice infected with doses of strept so tremendous there wasn't a serum in the world that could save them. And then Long, with Dr. Eleanor Bliss, saved those animals with prontosil and sulfanilamide—not 100 per cent, but most of them.

Long was a physician, a man who understood the whims of human patients, but this Eleanor Bliss, who was in the social register, a Bryn Mawr graduate, and a member of the First Families of Baltimore, knew laboratory animals. When she proved these magic drugs worked on mice, that was all Long needed. A week later, on the eighth of September, he jumped from the laboratory to the wards.

There was a little eight-year-old girl there, her skin flaming with erysipelas, her fever 106. She'd been given blood transfusions,

serums, and everything else in the medical cabinet, and she was dying. They gave her prontosil, repeating the dose every four hours; within eight hours that flaming redness had left her skin; and in thirty-six hours her fever was gone.

There was a woman with "infected abortion" penned on her chart, plus the warning notes—pelvic peritonitis, temperature 106.4. She, too, was dying. Sulfanilamide saved her in seventeen hours.

There was a little boy, only two, with erysipelas of the leg—a youngster with a bad case of scarlet fever—a young woman with acute tonsillitis—a man whose eye was seething with murderous bugs. Day after day, the nurses added the same phrase to their bedside records—*recovery uneventful!*

Drs. Long and Bliss weren't the first Americans to witness these miracles. A few doctors had heard about prontosil and ordered it from Germany. A few others had heard about sulfanilamide and got a few ounces from Du Pont's research laboratories. The Hopkins workers, however, were performing their miracles not on one or two isolated cases, but on scores of patients. They treated childbed fevers and middle-ear infection, peritonitis and blood poisonings, scarlet fever and impetigo, and they knocked the accepted mortality rates for a loop. They tried sulfanilamide even on the deadly streptococcic meningitis (mortality 99 per cent) and cured thirty-six out of forty-three patients.

For a few weeks, all this was kept within the confines of Baltimore. Long and his group of surprised miracle men kept their records to themselves, and only a handful of outsiders even knew the work was going on. Then one day the cork was pulled.

Around Johns Hopkins, Perrin Long had the reputation of being a staunch New Dealer, and around Johns Hopkins any New Dealer was considered fair game. One afternoon in his laboratory, so the story goes, Long was defending himself against the sarcastic taunts of his more reactionary colleagues, when in walked a secretary.

"Pardon me, Dr. Long," she said. "Long distance is trying to reach you."

"Oh, dammit. Well, who's calling?"

"Mrs. Roosevelt."

"Mrs. Roosevelt?" Long looked at the grinning faces of his friends. A little too obvious! He turned back to the secretary. "Tell Eleanor I'm busy now. I'll give her a ring next year."

Out went the secretary. "Ver-ry funny!" remarked Long. "That wasn't so subtle, you know. You boys'll have to be smarter than that!"

The other men merely smiled.

Back came the secretary. "Dr. Long, I'm sorry to keep bothering you, but Mrs. Roosevelt is . . ."

"Sure, sure, I know. Well, it's a good joke, and it's all finished. Run along and tell 'em it didn't work."

Out went the secretary.

All during the afternoon, long distance kept on with its frantic appeal for Dr. Perrin Long, but Dr. Long didn't want to play. Finally he decided he'd end this joking once and for all. He strode to the phone, yanked it off the desk, and shouted—"Hello! Yes, I'll take the call. . . . All right, now listen to me, wise guy. . . ."

And through the receiver came the voice familiar to ten million radio listeners. "Hello, Dr. Long. This is Eleanor Roosevelt calling. I've been trying to reach you all afternoon. They think my son is dying. . . ."

Perrin Long collapsed into a seat, whispered "God Almighty!" and said, "Yes, Mrs. Roosevelt. What can I do?"

Up in Boston, husky young Franklin Delano Roosevelt, Jr., was lying in the Massachusetts General Hospital, his mother and his fiancée, Ethel du Pont, at his bedside.

Starting from an infected sinus, the strepts had begun to spread through his body. His doctor, George Tobey, knew an operation was necessary, but dared not perform surgery with those virulent microbes running wild.

Day by day, the bulletins grew more ominous, and people re-

marked it had been the strepts that took the life of another president's son, Calvin Coolidge, Jr.

Newspaper reporters, dogging Dr. Tobey and the two frantic women, stayed glued to the hospital. And then suddenly one morning Dr. Tobey smiled and gave his statement to the press. "The boy is out of danger. . . . We can thank a new drug, prontosil."

By the next morning the names of prontosil and sulfanilamide were in every newspaper in the country. People read, marveled at the new wonders of science, and beseeched their own doctors to use the drugs on their sick and dying mothers, sons, cousins, and friends.

Young Roosevelt, statistically speaking, wasn't important. He was only one case in a long, long series. But he was the son of the President, and the magic drug that saved his life was front-page news. It made patients demand the treatment, and it made doctors use it. It brought sudden, embarrassing, handicapping publicity to Perrin Long and Eleanor Bliss.

"Good Lord!" they exclaimed. "We didn't discover the stuff, we're only using it!"

And using it they were. Perrin Long and dynamic Francis Schwentker and the rest of the doctors were snatching patients out of the grave, curing streptococcus infections and epidemic meningitis and even gonorrhea. Behind them in the laboratory, Eleanor Bliss was leading the way with animal experiments, and careful E. K. Marshall, Jr., was building up the sound, fundamental knowledge of how the drugs worked. Behind the physicians, still other researchers began to tamper with the chemistry of these compounds, seeking other and perhaps better modifications which might eventually replace these pioneer sulfa-drugs.

Prontosil gradually began to fade out of the picture, yielding to sulfanilamide, which was cheaper and more available and able to do anything that prontosil could. Sulfanilamide appeared to be perfectly safe—so safe it was used as much as a thermometer or a bedpan.

"The darn drug is ruining the art of diagnosis," some doctors complained. "Nowadays they're giving sulfanilamide to everybody who comes into the hospitals. Only if they aren't cured in four days do they even get a physical examination!"

Then sulfanilamide flashed in the headlines again.

Down in Tennessee, there was a little factory which put out a line of veterinary medicines, the sort of preparations advocated as being good for man and beast. The owner of the factory got a new idea one day, an idea which he thought was the best he'd ever produced—he knew that Southerners liked their medicine in liquid form, that sulfanilamide was available only in dry tablets, that sulfanilamide was being praised to the skies as a twenty-four-hour cure for gonorrhea, and that there was plenty of gonorrhea in the South.

There were the basic ingredients of his idea, and he set his chemists to find something that would dissolve sulfanilamide.

They found the drug wouldn't dissolve in water, and it wouldn't dissolve in alcohol, but it would dissolve in a newfangled solvent known as di-ethylene-glycol. The factory commenced turning out a solution of sulfanilamide in di-ethylene-glycol, a product which was labeled *Elixir of Sulfanilamide*. . . .

One Monday morning, Dr. Morris Fishbein walked into his American Medical Association office in Chicago and picked up a telegram from Tulsa, Oklahoma—six people had died, all with the same unmistakable signs of kidney damage. All had taken doses of an Elixir of Sulfanilamide. What was in that Elixir?

Dr. Fishbein did not know, but he meant to find out. Off went a telegram to the factory asking for the composition of the product.

The factory people weren't very co-operative and at first refused to answer, but finally they admitted the Elixir consisted primarily of sulfanilamide dissolved in di-ethylene-glycol. They offered that information with the request that it be kept secret—after all, they didn't want their clever formula stolen by competitors—but Fishbein ignored their plea. Immediately he wired Oklahoma that the deaths were undoubtedly caused by the di-ethylene-glycol.

The word was passed on to Washington, and at once the Federal Food and Drug Administration hurled its force against this menace. There were thousands of bottles of the reddish, raspberry-flavored Elixir of Sulfanilamide at large—on drugstore shelves, in doctors' offices, even in bathroom cabinets. Every one of them was liquid death. The federal men were ordered to confiscate first and ask questions later.

Too late the factory officials learned what had happened and tried to protect themselves. They turned to the American Medical Association: PLEASE WIRE COLLECT WESTERN UNION SUGGESTIONS FOR ANTIDOTE AND TREATMENT FOLLOWING USE ELIXIR SULFANILAMIDE.

Back came the answer: ANTIDOTE . . . NOT KNOWN.

Radio, newspapers, and posters flooded the South with warnings: "Danger! Do not use Elixir of Sulfanilamide!" But the warnings, too, were late. Even before the federal inspectors went into action, too many bottles had been dispensed and used. Too many telegrams still poured into the American Medical Association offices—sixteen deaths in Mississippi, five in Texas, five in South Carolina, nine in Oklahoma, seven in southern Illinois, seven in Georgia. . . .

At the end, the federal men had performed the almost unbelievable feat of rounding up every single bottle. They had done this in spite of the fact that jittery salesmen lied about their customers, hysterical druggists altered their records, and panicky physicians crept into pharmacies at night to destroy their prescriptions.

The known deaths totaled nearly eighty, the unreported fatalities possibly a hundred more—all caused entirely by one company's ignorance.

Every one of those deaths was unnecessary and avoidable and bitterly tragic. One Oklahoma woman wrote her story to the President of the United States:

"Dear Sir: Two months ago I was happy and working taking care of my two little girls, Joan age 6 and Jean age 9. Our by-word through the depression was that we had good health and each other. Joan thought her mother was right in everything. . . . To-

night, Mr. Roosevelt, that little voice is stilled. The first time I ever had occasion to call in a doctor for her and she was given Elixir of Sulfanilamide. Tonight our little home is bleak and full of despair. All that is left to us is the caring for of that little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. . . ."

And all they could do to the manufacturer under the law as it then stood (but no longer stands today) was penalize him for mislabeling his bottles. According to law, an "elixir" is something dissolved in alcohol. Di-ethylene-glycol is not alcohol.

"My chemists and I deeply regret the fatal results," the manufacturer told reporters, "but . . . I do not feel there was any responsibility on our part."

His chief chemist, however, had a different kind of conscience and a more vivid imagination. He committed suicide.

V

Improvements on sulfanilamide went more cautiously in other laboratories and other countries. German chemists of the I. G. prepared more than a thousand new derivatives but failed to find one any better than sulfanilamide. Additional hundreds were made in France, tested, and discarded.

Chemists of England's May and Baker Company tried scores of derivatives and finally came to number 693. May and Baker's 693 was very definitely not to be discarded. This chemical, a combination of sulfanilamide and pyridine now known as *sulfapyridine*, could do things that stumped even sulfanilamide. Sulfapyridine was the first of these new drugs that could really massacre pneumonia microbes.

Distinguished researcher Lionel Whitby reported from London that sulfapyridine protected mice from ten thousand lethal doses of the pneumococci. Drs. G. M. Evans and Wilfrid Gaisford of the Dudley Road Hospital in Birmingham tried it on human patients

and announced it was the answer to a physician's prayer. Given orally in the form of bitter tablets, it quickly stopped the fever and cut the mortality rate in half. And, unlike antipneumonia serum treatments, which require a specific type of serum for each one of the fifty-odd types of pneumonia germs, sulfapyridine worked on all types.

The world soon heard that sulfapyridine could throttle its old enemy, that it was "no longer necessary to die from pneumonia."

And then, down in Africa, sulfapyridine taught scientists that this business of drug-hunting requires not only good drugs and good doctors, but also one additional ingredient—luck.

Early in 1939, three English doctors faced the outbreak of a fearful spinal meningitis epidemic in the Anglo-Egyptian Sudan, far south of Khartoum. This disease had struck the Sudan each year since 1935, hitting twenty-one thousand patients and killing nearly fifteen thousand, and the 1939 outbreak started out more violently than any of its predecessors.

There weren't great hospitals in the Sudan, nor scrupulously clean medical centers, nor purring electric refrigerators where meningitis antitoxin could be stored. There weren't splendid libraries where the newest facts on meningitis were available in neatly catalogued journals.

But in the little hospital at Wau, there were three small sample bottles, not of sulfapyridine, but of sulfanilamide.

Hell began to break loose early in January.

"This one," confided Dr. Joseph Bryant, "is going to be a stinker —too many coughs and colds already all over the district, and the bloody natives soured on us since we couldn't save 'em last year. Well, Fairman and I might as well go down into the Dinka districts. Usher Somers will have to cover Rumbek."

So these three men pushed off just as the storm broke. Within three days, there were forty-one cases with thirty-three deaths—a mortality rate of 80 per cent! This was going to be wonderful. . . .

There were the usual things that could be done—police the roads and river crossings, shut the merchants' shops, disband the

crowds of gossipers, try to call off native dances and ceremonials.

And there were those three bottles of sulfanilamide. "Want to try them?" asked Fairman. "Stuff's supposed to hit meningos."

"Might as well," Bryant agreed. "Hope we don't have too much trouble getting the beggars to stand still for injections."

"Injections? I thought you give sulfanilamide by mouth."

"Really? Did you ever try to force anything through the mouth of one of those big Dinkas, particularly when the disease has his back arched like a bow and his teeth jammed together like a vise? No good, old boy. We inject or we don't use it."

The epidemic got worse, and the natives didn't want injections. The weather was nasty, too, with bitter cold nights, roasting days, and a strong north wind that kicked clouds of dust into the air, day and night. Tempers got short, and maybe the tempers did it—there had been three little bottles of sulfanilamide, but when sterilization was finished, two bottles had smashed.

"Nice going," muttered Fairman. "What do we do now?"

"Use the last bottle, anyhow. Let's see what happens."

They tried that last bottle on a few natives who would stand for injections. They pumped the drug into their muscles, under their skins, even directly into the spinal canal. *And those natives got better!*

A few hours after the injections, the patients began breathing more easily. Their eyes, once wide and glazed, closed in restful sleep. Their delirium disappeared, and they began to talk rationally. Patients who had been crippled and half out of their minds in the morning could walk and talk sensibly by nightfall.

Bryant and Fairman treated twenty-one patients and cured twenty of them, and that was the end of that last little bottle of sulfanilamide.

"Good fun while it lasted. Now what?"

"I say!" said Fairman. "There's nearly a pound of sulfapyridine back at the hospital!"

"Sulfanilamide, you mean."

"No, sulfapyridine. May and Baker sent us a big sample to try on pneumonia. They say it's topping stuff."

Bryant nodded sagaciously. "Don't doubt it, old boy, but stick to the matter at hand. This isn't pneumonia—it's meningitis!"

"Um-hm. That's a very good point. But look here—old M and B say it's for pneumos. But they *don't* say it's *not* for meningos."

Bryant nodded again. "Well, that's a point, too. So you think we ought to use this sulfapyridine?"

"Why not?"

"Right-o!"

So Bryant and Fairman started to use sulfapyridine as their last chip in a gamble with death. Sulfapyridine might kill the poor Dinkas, but the doctors knew that unless something were done, the Dinkas were sure to die from meningitis anyway.

They explained the odds to the third member of their staff, Dr. Somers of the Rumbek district, and Somers admitted the idea had a faint glimmer of merit. "But how do you give the beastly stuff?" he asked. "What's the dosage? What's the toxicity?"

Bryant and Fairman offered no help. "If *you* find out," they suggested, "you'd better tell *us*. This is what our friends at home would call research. Only we're using natives instead of guinea pigs, and we might catch the rotten infection ourselves!"

"Don't be so damned heroic," Somers snorted. "You sound like a journalist. If I find anything, I'll let you know. . . ."

Somers went back to Rumbek, and Fairman and Bryant started again on the Dinkas.

There was a human problem that still had them blocked, and Fairman put his finger on it quickly. "How are we going to use this sulfapyridine if we can't get any patients? They get sick in the villages, but they don't come to us. They go to their bloody native medicine men instead and listen to a lot of mumbo jumbo. Can't we do something?"

"I don't know. Those medicine men are tricky devils, jealous and suspicious. What can we do?"

"Haven't the slightest idea," Fairman answered. "But if we don't do something, they're going to put us out of business. I say, mayn't we have a word with the beggars?"

"Quite so," Bryant agreed. "I know one old boy in the next village. Let's see what he wants to keep his ugly thumb out of the pudding. . . ."

The Englishmen called on their first dusky colleague and then on another and another. Visiting at village after village, they drove along the hot, dusty roads. They palavered with the native witch doctors, explained, bribed, cursed, promised, threatened, cajoled, offered anything under the blazing Sudanese sun. The medicine men listened, agreed to nothing, but retired to consider the propositions.

In their steaming, bouncing little car, Bryant and Fairman started to drive back. The whole business looked hopeless. Then Bryant suddenly took his foot off the throttle and coasted to a stop.

"There's a native girl over there under the bush. Got a child with her. Be a good lad and see what she wants."

Fairman cursed and climbed out of the car. In a minute he was back, grinning. "She's got a sick kid with her, all right. Meningitis. Says her medicine man told her about us—said we have a new 'magic in a bottle' to kill the devils in her baby. Pass me the kit, will you? I think we have a patient!"

"Magic in a bottle," repeated Bryant. "I say, that's rather good!"

The little native baby was the first of a horde of clients. Treating patients who had been dragged and carried to the side of the road, the two doctors performed their devil-slaying all that day and for many more days. Some patients came from near-by villages, others had been brought from twenty miles away. There were men and women, babies and grandparents, some in the first stages of the disease and some nearly dead. The natives knew meningitis only too well and could recognize its symptoms as fast as the best Harley Street specialists. Bryant and Fairman had no complaint now about the native doctors—the medicine men had sold the new magic to the people.

Cursing in tired profanity as the gooey drug, much too warm, clogged his hypodermic needles, Somers used sulfapyridine on his patients in Rumbek at the same time. He treated his patients under trees, in dusty grass shelters, out in the bush country far from roads, and with only the help of willing, but too few and too ignorant, natives. He was forced to depend on a primitive version of field-hospital nursing—one relative of each patient was allowed in to look after and feed the sick.

When the Englishmen finally had time to compare notes, they found the native medicine men had not overpraised the new drug. Somers had treated nearly one hundred and fifty patients and expected to see about a hundred and twenty die before his eyes. He lost only fourteen.

Bryant and Fairman had treated nearly two hundred and lost only nine.

The mortality rate had been sliced from 80 per cent down to less than 10 per cent.

The doctors got together and wrote up their results and sent them off to London for publication. They were the strangest reports that European and American scientists had ever seen:

"Apologies are hardly needed for the omission of microscopical examinations and temperature records. The methods used were in the nature of desperate remedies and may perhaps be new. . . .

"We are indebted to the Director of the Sudan Medical Service for permission to publish this paper . . . and to the numerous Sudanese dressers who willingly entered into the treatment of this dangerous and infectious disease in overcrowded, dark, and airless huts. . . .

"And we give thanks to the many nameless Dinka 'medicine men' who forsook their own lucrative practices and used their authority in encouraging patients to come to us."

Good drugs, good doctors—and good luck!

Eventually sulfanilamide and sulfapyridine, like prontosil before them, were generally discarded. They had served heroically, saving hundreds and hundreds of thousands of lives. But they were

not perfect, not safe enough nor effective enough, and better ones took their place—*sulfathiazole* and *sulfadiazine* and *sulfaguanidine* and a host of other sulfa-drugs. Yet even these improved forms had their limitations; they were not completely safe, and there were still microbes which they couldn't touch.

The drug-hunters needed another lucky break.

CHAPTER XI

Miraculous Accident

FLEMING, FLOREY, AND PENICILLIN

It was a pleasant London pub, just across the street from dingy old St. Mary's Hospital, with potted palms, and a warm, pervading odor of beer, and the talk of men stopping for a quick one on their way to supper.

The stocky little white-haired man finished his glass of bitters, absent-mindedly nodded good night, and moved quietly toward the door.

As he passed a table, Mr. Peters looked up, waved, and said, "Good night, doctor."

"Eh?" said the white-haired man. "Yes, yes, of course. Good night." And he went out into the night, where searchlight beams were already looking for Nazi bombers.

Back at the table, Mrs. McMullens was curious. " 'Oo's yer pal, Mr. Peters?"

" 'Im? That little man," announced Mr. Peters, "is Alexander Fleming. Professor over at the ruddy 'ospital, but 'e's smart, too. 'E's the man what hinvented penicillin."

Mr. Jeremiah Coots expressed disbelief. " 'E did not! I know fer a ruddy fact that penicillin was hinvented by a professor at Oxford. Fellow by name of Florey."

Mrs. McMullens removed a bit of beer foam from her upper lip. "Yer both wrong," she said. "I 'appen ter be in a position ter know that if it weren't fer that narsty 'Itler . . ."

Fleming and Florey—and maybe Hitler. They made the story of penicillin.

It seemed there had always been Flemings around the Scotch city of Kilmarnock. They were merchants and farmers, they wove fine curtains and carpets on their hand looms, they raised cattle and they sold milk and they made cheese as good as any to be found throughout Ayrshire.

Hugh Fleming's farm was near Darvel, not quite ten miles from Kilmarnock, on the banks of Irvine Water. He was a good, honest Scotsman, and he taught his children to use their eyes and their brains, to be patient and thrifty, and to fear God. On August 6, 1881, his wife presented him with a new son, who was named Alexander.

As a boy, young Alexander was considered a reasonably good student—perhaps a wee bit better than some—but nothing to set the world on fire. He was good at games, an excellent swimmer. When he was ready for a further education, he was sent to Kilmarnock Academy.

"Study your lessons well, Alex," his father told him. "Maybe we can make you a doctor like your brother."

Alex studied his lessons very well. When he finished at the Academy, he went to London and worked in a shipping office, and then decided he was ready to tackle medicine.

"Where should you like to go?" his brother asked him. "To Edinburgh, perhaps, or Oxford?"

"No," said Alex, "I've about made up my mind to stay here in London and go to St. Mary's."

"St. Mary's? But why? It's not the best school . . ."

Alex nodded. "I know, but I understand it won the Rugger cup last year, and it's got a championship swimming team."

So, at the age of twenty-one, Alexander Fleming entered a competition for a scholarship at St. Mary's Hospital Medical School, won it, and became a medical student. It was not a very remunerative scholarship, and St. Mary's was not a very top-notch medical school, but Fleming was satisfied. When he graduated in 1908, he

walked off with honors in physiology, pharmacology, medicine, pathology, forensic medicine, and hygiene, and the University Gold Medal.

"What will you do now?" his friends asked him. "Back to Scotland and start looking for patients?"

Fleming shook his head. "Not just yet. I've a mind to stay here and do a little research."

But what kind of research? Fleming had no particular ideas. One day soon after his graduation, he heard of a vacancy in St. Mary's bacteriology department under Sir Almroth Wright, and although he wasn't particularly interested in bacteriology, he applied for the job and got it.

In those days the faculty of St. Mary's was not altogether distinguished; it was, in fact, rather second-rate, but Wright was one of the exceptions. For more than a decade, he had been working on the microbes that infect the intestinal tract of man and animals, he had led the war against typhoid fever, and now he had succeeded in introducing a vaccine to prevent typhoid.

"What do you know about bacteria?" he asked Fleming.

"Very little, sir."

"Excellent," said Wright. "You'll do."

Under Wright's tutelage, Fleming began to learn about bacteria—about the ways in which they invade and attack the human body, about the body's defense system, about white blood cells, about antiseptics and serums and vaccines. He set up simple experiments, none of them very important, and he helped teach the medical students.

When World War I broke out, he went into the army medical corps with a captain's commission and was sent to Boulogne to work in the British Expeditionary Force's 13th General Hospital.

"Your job is to find an improved wound antiseptic," he was told. "Our men are dying from infections. The antiseptics we have aren't good enough. See what you can do."

Carrying out these instructions, Fleming began to look for "an improved wound antiseptic." How do you find such a thing? Well,

you get bottles and vials and packets of all sorts of chemicals, and see what they do to germs. For months Fleming did exactly this. So did many of his fellow scientists. And none of them found anything that looked like a superior antiseptic. Fleming did one other thing—just for curiosity, he tested some of the standard antiseptics and some of the proposed new ones on living human cells, on the white blood corpuscles that act as the body's defense system.

"Isn't it odd," he remarked, "that some of these chemicals are better at destroying white blood cells than at killing germs? I shouldn't think they would be very practical."

Unfortunately, it was only too true that many of the harsh antiseptics already in use were almost as deadly to the patient as to the invading germs. But Fleming didn't see what he could do about it. He served out the war in his army laboratory, and then came back to St. Mary's in London. For several years he kept on with his work, teaching a few classes, trying a few not-too-exciting experiments, occasionally writing a not-too-exciting paper for the scientific journals. All along, in a very mild way, he kept on the watch for a nontoxic germ-killer—a lifesaving substance which would destroy microbes without harming healthy human tissues.

In 1922 he thought he had one. It was a substance which he called lysozyme—a microbe-dissolving chemical which he could detect in human tears, in saliva, and even in egg whites. But lysozyme was not very useful, for the microbes it could destroy were not the microbes which cause disease.

The few doctors who bothered to read his report were not greatly impressed. One of them remarked, "I have enough trouble with dangerous microbes without worrying about harmless ones."

Fleming kept on with his researches. Two years later, in 1924, he worked out a novel method to measure the probable usefulness of any antiseptic. First, he said, you should measure the effect of the antiseptic on microbes and see how much it takes to kill them; second, measure the effect on white blood corpuscles, the body's own germ-digesters. If the antiseptic is more toxic to white blood

corpuscles than to germs, then it probably won't be very useful, but if it can kill germs without killing white blood cells, then it might be an antiseptic with real medical value.

Four more years went by and a publisher wrote to him: "We want to bring out a new book on bacteriology. Will you write the chapter on the staphylococci?"

It was a perfectly ordinary request, and quite a proper one, for Fleming was now the director of St. Mary's inoculation department and had become an admitted expert on the pus-forming staphylococci, the deadly little germs that grow in grapelike clusters and cause such annoying things as boils and carbuncles—and also deadly infections of the spine, the heart, and the blood.

It was an ordinary request, this note from the publisher, but it was the first in a series of accidents and coincidences that were unparalleled in the history of drugs.

Fleming replied that he would be glad to write the chapter, and set about getting his ideas and his notes into shape. There was one little experiment he wanted to try, too, before he did his writing; he'd just read a report which said that, under certain circumstances, colonies of these staphylococci could change their appearance.

"Remarkable if true," Fleming mused. "But I should like to see this myself."

So, one day in the summer of 1928, the little, blue-eyed Scotch scientist began filling sterilized glass plates with sterilized jelly, covering them with sterilized glass tops, and then—when everything was ready—lifting off the covers, planting a few staphylococci, and whipping the covers back. This was the time-honored procedure to prevent contamination, to keep unwanted microbes out of the picture, and it was especially necessary in Fleming's little laboratory, for his workroom was not like the gleaming, polished, ultra-ultrasterile laboratories of the big institutes; it was dark and it was crowded and it was not—as Fleming himself often complained—quite clean.

Weeks went by, and more and more plates of staphylococci were

piled on the long table next to the window. It was September, hot and sticky, and the window was open. . . .

Fleming reached for one of the dishes of staphylococci.

"Here's a new one," he remarked. "Wonder how it looks."

He quickly lifted off the cover glass, slid the plate under his clumsy dissecting microscope, looked for a few seconds, and then put back the cover. How long had the cover been off? Two seconds? Five seconds? Ten? Whatever it was, it had been long enough.

A few days passed and once again Fleming came upon the plate. At first glance it seemed to be all right. And then . . .

"Damn! Something has got into this one."

Inside the plate, over to one side, a speck of mold was growing—growing right on top of a colony of staphylococci. It was white and fluffy, somewhat like bread mold, with a touch of dark green in the center.

"Well, this plate's ruined. Out it goes."

In hundreds, perhaps thousands of laboratories, just such an accident has happened—a cover removed for only a second too long, a spore wafted in by a breeze, and, in a few days, a contaminating growth of mold. And in all those laboratories, the next step had inevitably been the same— "You use the appropriate language," he said, "and chuck the contaminated plate into the sink."

He was ready to toss out this plate—and millions of human lives waited in the balance. But he stopped.

"Might as well take a look at it first," he thought.

He looked and saw a miracle. It didn't look like a miracle, of course; what he saw was a colony of mold growing on top of what had been a big colony of deadly staphylococci. Away from the mold, the staphylococci were still growing luxuriantly in moist, buttery little mounds. But around the mold there was a clear zone —*a zone in which the staphylococci were obviously being dissolved!*

"Now, that's very odd," he murmured. "I've never seen a mold do that before!"

Another scientist might have wondered about this for a moment, and then proceeded to discard the contaminated plate and forget about it. Fleming, however, was not another scientist; he decided to look into this mold. Picking up a platinum wire, he sterilized it in a burner flame, let it cool, deftly touched it to the mold and transplanted a bit of this to a fresh tube of microbe food. Then, for weeks, he grew and studied it; he transplanted it again and again, sometimes to other tubes and sometimes to bottles of broth.

"In broth," he wrote, "it grows on the surface as a white, fluffy growth; in a few days, this becomes a dark-green, felted mass. In a few weeks, the broth becomes bright yellow."

This yellow color, whatever it was—could that be the stuff that dissolved the staphylococci? Soon Fleming found that the yellow matter had nothing to do with germ-killing. "It is only an impurity," he wrote in his notebook, "but it does give a nice yellow color."

Mixed with the yellow stuff was something else, a second substance which was also secreted by the mold and which also soaked all through the broth. Fleming poured off some of this broth, mixed it with colonies of staphylococci, and found that it stopped their growth. He tried it on streptococci—and it stopped them, too. It destroyed the microbes of pneumonia, diphtheria, meningitis, and gonorrhea. Against other germs—the microbes of cholera, dysentery, and typhoid—this "mold juice," as Fleming called it, was useless. It was not a complete germ-killer. When it did work, however, its power was astounding; even when the mold juice was diluted as much as eight hundred times, it could still destroy microbes. This juice, he calculated, was three times stronger than carbolic acid!

And then the thought, "Good Lord! Anything that strong will be murder to animals or human beings. It will wreck their tissues!"

He tried it. He put the mold juice through his test with white blood cells, and found that the white blood cells were unharmed. He injected more than half an ounce of the undiluted juice into a rabbit. The rabbit scarcely batted an eye.

Now Fleming realized what he had—a new, mysterious

chemical which was sheer murder to microbes but *virtually harmless to healthy tissues.*

The next step was to try it on human beings. He took some of the mold juice into the hospital wards, poured it into the raw, infected, sensitive wound of one patient, and into the eye of another. "There was no irritant effect," he reported.

But did it cure the infected wound or the sore eye? No, it did not —for the simple but unfortunate reason that Fleming and his colleague Mr. Ridley couldn't prepare enough of it to cure anything. Weeks were required for the mold to secrete enough of this stuff for even a small laboratory test. Furthermore, it was exceedingly unstable and lost its activity on the slightest excuse. Ridley tried to concentrate the material, and evaporated great quantities of the juice to a sticky mass, but he couldn't isolate the active chemical in pure form.

All they could do with it, apparently, was to name it. After Fleming had identified the mold as a member of the *Penicillium* family, the potent but still elusive microbe-killer was called *penicillin.*

"Someday," he remarked, "some chemist may come along and find out exactly what it is and manufacture it."

In May, 1929, after eight months of work, he wrote his first formal report—a simple, ten-page announcement which was eventually published in the *British Journal of Experimental Pathology*. As one of his conclusions, he wrote: "It is suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes."

In the next year or two, he managed to accumulate enough crude penicillin to try on a few infected wounds, chiefly carbuncles and infected sinuses. "Although the results were considered favorable," he said, "there was no miraculous success."

The publication of Fleming's paper made no great noise in the scientific world. Since the time of Pasteur, bacteriologists had suspected that various molds, fungi, bacteria, bacilli, and cocci produce substances which could destroy other microbes. Some of

these substances—pyocyanase, penicillic acid (no relation to penicillin) and actinomycetin—had actually been isolated and tested, but either they destroyed the wrong kind of germ or they were too toxic to human beings.

When scientists read the report on penicillin and noted first that it was murder against microbes, they said, "How splendid!" But when they read further and found that penicillin was practically impossible to produce in quantity, they concluded, "How unfortunate!" and most of them forgot all about it.

A few men wrote to Fleming for samples of his strain of mold, and they checked parts of his work. At the London School of Hygiene, a group of chemists headed by Harold Raistrick tried their hand at improving the extraction of penicillin, but they didn't get very far.

"Raistrick succeeded only up to a point," Fleming commented later. "The bacteriologists in his institution didn't seem to think much of his research, so they didn't co-operate. He was stuck for want of bacteriologists and we were stuck for want of chemists."

One might think that bacteriologist Fleming would have co-operated with chemist Raistrick, but somehow it didn't work out that way.

"When we saw that this good chemist had failed to extract penicillin," added Fleming, "we stopped doing anything about it. If he couldn't, we couldn't."

It was 1932 when Raistrick admitted that "he couldn't." On Christmas Day of that same year, Mietzsch and Klarer of the I. G. Farbenindustrie applied for a patent on a new chemical which they called prontosil. It was the first of the sulfa-drugs.

The sulfa-drugs could also kill microbes. They were not altogether safe. They could not touch some of the microbes that penicillin could hit. But you could produce the sulfa-drugs practically in any chemical laboratory—by the ounce, by the pound, by the ton.

Penicillin was a dead pigeon.

II

Howard Florey was a handsome young man who was good at everything. Born in Adelaide, Australia, in 1898, he was the son of a prominent boot manufacturer. He went to Kyre College and St. Peters Collegiate School, where he won a dozen prizes in chemistry, physics, mathematics, and history, and half a dozen scholarships. In 1917 he entered the medical school at the University of Adelaide, where he proceeded to be top man in his class for three out of four years.

Out of the classroom, he was equally prominent. He starred on the university's football, running, and tennis teams, he edited school magazines, and he was an excellent debater.

A young man like that, it was generally agreed, should not be permitted to waste his talents in an ordinary Australian doctor's office. In 1921 he sailed for England as a Rhodes scholar. Behind him he left a charming fellow medical student, Ethel Reed.

"I'll be back in three years," he told her.

He stayed at Oxford for three years, listening to lectures on physiology and pathology, studying the circulation of capillaries, the nature of inflammation, learning what happens to tissues when they get sick. Then he worked for a while at Cambridge, took time out to accompany a scientific expedition to Spitzbergen, came to America in 1925 as a Rockefeller fellow, and the next year returned to work at the London Hospital.

"I won't be coming back to Australia for a long time," he wrote to Ethel Reed. "Will you come to England?"

In Adelaide, Ethel had finished medical school and was a resident in the Children's Hospital. She was on her way up in Australian medical circles, but when Florey's letter arrived, she resigned and sailed for England to become Mrs. Howard Florey, housewife. Soon after their marriage, the Floreys moved to Cambridge, where Howard Florey lectured on pathology and started research on new substances which might kill germs.

Oddly enough, one of the first things he investigated was

lysozyme, the microbe-killer which Alexander Fleming had recently discovered in tears, saliva, and egg white. Fleming had already found that lysozyme could do a splendid job in assassinating harmless bacteria, but that it was useless against such deadly germs as the staphylococci, the streptococci, the pneumonia microbes, and the tubercle bacilli. Florey repeated the work and got exactly the same results.

"This man Fleming," remarked Florey, "seems to know his business."

In 1931 Florey left Cambridge to become a big frog in a rather small puddle—professor of pathology at the University of Sheffield.

During the next few years, strange things went on across the Channel in Germany. Adolf Hitler, the fanatic little house painter, organized his brown-shirted bullies and began to shriek and scream against the indignities which had been heaped upon the Fatherland, to move closer and closer to the dying Hindenburg. Early in 1933 Hitler was named chancellor, and laws were soon drafted to "reduce the percentage" of Jews in government, in industry, in law, in medicine, and in science. By summer, thousands of Jews and other political refugees were leaving Germany to find a foreign haven.

Among those who got out was twenty-seven-year-old Ernst Boris Chain, part Russian, part German, one of the most promising young chemists in the Reich. Chain had been born in Berlin, studied chemistry and physiology at the university there, and then gone to work in the department of pathology at Berlin's great Charité Hospital. He worked on enzymes and complicated organic chemicals, on yeasts and bacteria and tissue cultures. His superiors predicted a brilliant future for him, but he saw clearly what was coming in Germany.

"I shall have to go," he said at the hospital. "It is better for me to move to France, or perhaps England."

His superiors tried to reassure him. "You mustn't think of it!" they told him. "This is just a passing phase. It will all be over in a

few months. And in any case, nothing could happen to you—you're a scientist, and Germany has always taken care of her scientists."

Chain decided he would prefer to take care of himself. He left Germany and went to Cambridge University in England, where the old vitamin-hunter, Sir Frederick Gowland Hopkins, gave him a place in his laboratory. Two years later, in 1935, Howard Florey —who had just been named professor of pathology at Oxford— came to Cambridge looking for a chemist. On Hopkins' recommendation, he took Chain.

Florey and Chain became friends and coworkers. They discussed each other's laboratory investigations. They answered each other's questions, Florey drawing on his excellent knowledge of tissues and disease, Chain providing new tricks in chemistry. They talked about the new wonder drugs, sulfanilamide and its cousins, which were so amazing, so miraculous, so completely practical. But the sulfas couldn't cure tuberculosis or syphilis or many other diseases. Sometimes the sulfas cured a patient of a simple streptococcus or pneumonia infection only to damage his kidneys. And sometimes there appeared a strain of streptococci or staphylococci which was untouched by the sulfas.

The sulfa-drugs, they agreed, represented a tremendous advance. But they also agreed that medicine needed something better.

The something came from Fleming's work, not on penicillin but on lysozyme. Florey and Chain had been following that old scientific will-o'-the-wisp, and one day came to the decision that they should look into other antibacterial substances, perhaps some produced by microbes and fungi and other microorganisms. Chain and his young American assistant, Leslie Falk, began reading the old reports on actinomycetin and pyocyanase and bacteriophage. Finally they came upon the first report on penicillin which Alexander Fleming had written back in 1929.

"This is very curious," said Chain. "Eight years ago this man found a splendid substance. I wonder why he didn't do any more with it."

Falk read the report. "Maybe because it was too tricky to handle," he suggested. "Looks like one of those impossible chemicals."

"No," said Chain, "not impossible. Perhaps a very difficult chemical, but not an impossible one. Maybe we should speak to Dr. Florey."

Operations in Chain's chemical laboratory got off to a slow start. He began growing Fleming's mold, repeating the first simple experiments in test tubes. The research was constantly interrupted by work on other laboratory projects, but nobody minded—after all, this was not a very vital job. It became vital suddenly one September morning in 1939 when a BBC broadcaster announced: "Hitler has invaded Poland." World War II was on.

Britain at war needed guns and planes and tanks. She also needed drugs—anesthetics and vaccines and especially microbe-killers to fight the plagues and wound infections which always accompany war.

What about penicillin? It was still an untried, untested, unisolated agent. Now, when there were scores of essential jobs for every trained scientist, did it justify a further investment of their time? Howard Florey thought it did. He not merely gave Chain his backing, but he assigned to the job one of his best assistants, Norman Heatley, thin as a scarecrow, so shy that he blushed when you said good morning to him, but almost unbelievably patient and skillful. Arthur Duncan Gardner, Oxford's professor of bacteriology, agreed to join the expanding penicillin team. Soon there came more chemists, biochemists, bacteriologists, and pathologists. More and more big earthenware jars were delivered to the laboratory and filled with more and more gallons of mold food. Shelves were packed with containers of ethers, alcohols, ketones, esters, and every other conceivable solvent that might be used to extract penicillin.

They found that penicillin is an acid, and that it is destroyed by contact with other acids. They found that penicillin can be extracted with ether or chloroform or amyl acetate, with its odor of

freshly crushed pears. And, of tremendous importance, Chain reported that there is a way to store penicillin.

"If you can get penicillin as a dry powder and keep it dry," he said, "it does not go bad. You can store it that way for weeks, months, maybe years."

In eight months, the war was going badly. Belgium and Holland had fallen, and British troops were beginning the bloody evacuation from Dunkirk. At Oxford, the local commander of the Home Guards checked again and again on his men, posting them each night to watch for Nazi parachutists. "It won't be long now," he warned.

In the Oxford laboratories, the penicillin-hunters kept grimly on with their work. They had already checked every step of Fleming's earlier study and now were far beyond it; they had tested penicillin for toxicity on rats, mice, cats, and dogs, and even on the sensitive brain tissues of a rabbit without getting any signs of irritation; they had run series after series of test-tube experiments, finding exactly which microbes could be stopped by penicillin and which ones couldn't. And finally they had extracted enough moderately purified penicillin—a dirty, brown powder—to try on microbes. Not microbes in a test tube this time, but germs rampaging through the blood and tissues of infected animals.

Florey sat in on that first animal test, the test which might brand these past months as a criminal waste of time. He watched eight sleek, healthy white mice taken from a cage and each given a huge injection of living, virulent microbes.

Four of those mice got nothing else. They were the controls, fated to die.

The other four got penicillin, injected every three hours, all night long.

"I must confess," he wrote afterward, "that it was one of the more exciting moments when we found in the morning that all the untreated mice were dead and all the penicillin-treated ones alive."

Penicillin had cured its first patients—four white mice.

With their tiny stock of penicillin, the scientists tried similar experiments and counted up at the end that the magic chemical had saved twenty-one out of twenty-four animals infected with streptococci, twenty-four out of twenty-five infected with a specially vicious strain of staphylococci, and twenty-four out of twenty-five infected with the gas-gangrene microbe.

In a brief report to the medical journal *Lancet*, they wrote: "The results are clear-cut. The antibacterial activity of penicillin is very great."

Now they wanted to go into the hospital wards, to try their brown powder on human patients, but there was no more penicillin —the mouse tests had taken it all. The men went back to work. Day by day, as the victorious Nazi armies swept across Europe and the threat of invasion came increasingly close to England, the Oxford scientists stuck to their benches. They poured more gallons of culture medium into their flasks and jars. They planted the mold again and again, tended it carefully as it grew, then drained off the broth and went through the long, tedious process of extraction. France collapsed, the Vichy government took over, and France broke off diplomatic relations with Britain.

"I wonder how much medicine you forget in fifteen years," Ethel Florey said to her husband.

"I don't know," he answered. "Why?"

"Oh, I'm going to start practice again. I think I shall be needed."

"You'll be needed," Florey said. "But what about the children?"

Mrs. Florey had her plans already made. "The faculty at Yale have offered to take care of all the Oxford faculty children for the duration," she said. "I think we should send Paquita and Charles to America."

The two Florey children, with some hundred and twenty other Oxford youngsters, were packed off to Yale University, and Mrs. Florey—Dr. Ethel Florey—returned to the practice of medicine.

Two months later, the Luftwaffe opened the Battle of Britain,

dropping terrible cascades of bombs each night on England's chief cities. At Oxford, the chemists learned that penicillin is destroyed by contact with certain metals and they began to grow it in shallow, enamel-coated containers—hospital bedpans.

The Italians invaded Greece, and the British went on the offense in North Africa and invaded Libya. At Oxford, Florey had put his entire department on penicillin. Now he was getting penicillin infinitely more pure than the earlier batches, and the power of this concentrated stuff was staggering—diluted a million to one, it could still kill microbes!

Each day the little pile of purified penicillin grew larger. "It won't be long," Florey predicted. "A few months more, and we'll be ready for clinical tests."

Early in February of 1941, after nearly two years of hard work, the pile of penicillin seemed large enough to treat one human patient. How do you choose the first patient? You take your new, untested drug into the wards and say, "I've got something which I think is good. Have you got a patient you'd like to try it on?" Usually, you get a patient who is about dead. Everything else has been tried on him, and now you're expected to bring him back from the grave.

Dr. Charles Fletcher was selected to give the first treatment. When he took his vial of penicillin over to the Radcliffe Infirmary, the doctors there picked out their man—an Oxford policeman, forty-three years old, who had been in the hospital for four months. He had come in with a little sore at the corner of his mouth—a sore which stubbornly refused to heal and instead began to spread. Sulfa-drugs did him no good; his was a breed of germs which were resistant to sulfas. Now he was dying from a combined staphylococcus and streptococcus infection of his face, scalp, both eyes, lungs, bones, and blood.

"All right," said the infirmary physicians, "let's see you do something for him."

Fletcher examined the policeman. He was emaciated, moaning in pain, too weak even to lift an arm. He was coughing up pus. In

spite of blood transfusions, his blood count was almost at rock bottom.

"Look here!" protested Fletcher. "This chap's nearly dead!"

"That's right," admitted one of the staff doctors. "We give him another twelve hours. Perhaps twenty-four. Of course, if you want an easy one, we could get you some fellow with a little boil on his neck."

"No, we'll go ahead with this man."

Fletcher took two hundred milligrams—less than one-hundredth of an ounce—of his white powder, dissolved it in water, sucked up the clear liquid in a syringe, and then injected it into the policeman's arm muscles. Three hours later, he put a shot of one hundred milligrams into the policeman's veins. All through the day, every three hours, another tiny dose of penicillin was injected. After the first twelve hours the patient was still alive—but that was the best you could say.

"We'll keep it up all night, every three hours," Fletcher said.

The next day a nurse, hardly believing it herself, wrote on the policeman's chart: "Striking improvement."

The policeman was not merely alive—he was getting better! His temperature was down a little, his pain was disappearing, his lungs sounded better, and the laboratory sent back an encouraging report on his blood count. Here, for the first time, penicillin was bringing a man back from the grave, but there was no jubilation in the wards. "At the time," Florey said later, "no one was much interested."

It was a Wednesday when they started the treatment. By Friday, even the regular hospital doctor was beaming. "In another week," he said, "the patient will be out of bed."

Another week? "Good Lord!" interrupted Fletcher. "We haven't got enough penicillin for another week. We thought we were about through."

They were by no means through. The policeman was amazingly better, but he was not cured, and the little stockpile of penicillin was almost exhausted. The scientists rushed back to the patient's

bedside. "Collect every ounce of this man's urine and send it over to the laboratory," they directed. "He's excreting a lot of penicillin through his kidneys. Maybe we can get some of it back."

Now they began a desperate attempt to get penicillin out of the policeman's urine, purify it, concentrate it again, and inject it back into him. "This is like trying to fill a bathtub with the plug out," observed Florey.

For a while this grotesque routine seemed to work. On Saturday, the nurse jotted down again, "Continued improvement." On Sunday, they had to interrupt treatment from noon to six o'clock at night until they could recapture more penicillin from the urine bottles, but the policeman was improving steadily, his blood count was climbing back, and one infected eye was practically normal.

On Monday, the nurse greeted the doctors with cheering news. "He's much better this morning," she announced. "His fever is all gone, the sores are healing nicely, and he's really quite hungry!"

"Splendid," murmured the doctors.

"What about the injections today? Do we continue the usual . . ."

"No," said the doctors. "No injections today. Or tomorrow. Or ever. We've run out of penicillin."

The nurse gasped. "But he's been doing so well! Can't you make some more?"

"It would take weeks, and he'll be dead by then."

He was.

"The attempt to treat this forlorn case was chiefly valuable in that it showed that penicillin could be given over a period of five days without significant toxic effect," Florey and his group reported. "Later experience showed that the dose of penicillin employed was too small, and the period of administration too short."

One vital lesson came out of the dramatic case of the dying policeman: *Give enough penicillin, and give it long enough, or you'll lose your patient.*

That lesson was underlined again a few weeks later when the

Oxford workers had built up another small stock of penicillin and went back for their second patient. This time it was a fifteen-year-old youth who had come into the hospital for a bone operation, suffered a severe hemorrhage, and then came down with a rampaging infection. The doctors gave him sulfas, too, but they didn't help.

"This fellow is failing rapidly," the staff doctors explained. "We've about given up hope. Want to try him?"

"Might as well," said Fletcher. "We've nothing to lose."

After five days of penicillin treatment, the patient was remarkably improved. Two ugly wounds on his hip were beginning to heal, color was coming back into his pale, hollow cheeks, and his temperature was normal.

But once more the penicillin ran out. After a few days, the infection blazed again.

To some observers, this entire penicillin research was a fantastic waste of men, money, and time. More than two full years had passed and not a single human life had been saved. Although the chemists had made one improvement after another, it was necessary to start with forty gallons of laboriously prepared "mold juice" and devote days of drudgery to extract enough penicillin to treat one patient for one day.

One expert, noting that the treatment in the first two cases had cost about a thousand dollars a day per patient, wrote: "At this moment, penicillin is to other antiseptics not unlike what radium is to other metals."

A learned professor described it to his students and remarked, "You should learn about this penicillin. Remarkable substance! They grow it in bedpans and purify it by passage through the Oxford police force."

Under the inspiring leadership of Florey and Chain, however, the Oxford scientists refused to quit. Sooner or later, they were convinced, their luck would turn. Meanwhile Florey brought in still more experts to speed the work; he got more money from the

British Medical Research Council and the Rockefeller Foundation; and, of particular importance, he induced Imperial Chemical Industries, Ltd., to help make penicillin in their laboratories.

By May of 1941, with Greece and Yugoslavia conquered by the Germans and London taking the worst bombing raids of the war, the Oxford workers were ready to try once again. Their next patient was a forty-eight-year-old workman, a thin, broken-down little fellow who had just come into the hospital with a huge carbuncle that was pouring murderous staphylococci into his body. They were festering in his nose and his lungs, swelling the glands in his armpits, and sending his temperature higher every hour.

With penicillin for seven days, Fletcher cured him.

At long last, penicillin had saved a human being.

The next patient, Number Four in the series, was another triumph for penicillin—but the patient died. He was a little four-year-old boy, semiconscious when brought to the hospital, his neck rigid, his eyes swollen, his spinal fluid swimming with staphylococci. Five weeks before, he had come down with what appeared to be an ordinary case of measles, but the measles were followed by a minor skin infection, and this minor infection suddenly exploded into a general disease with germs spreading all over his body. In three days of penicillin treatment, he was obviously better; in nine days he was talking and playing with his toys; but on the eighteenth day he died. Autopsy showed the penicillin had stopped the germs all right. Death had been caused by a ruptured blood vessel.

"Before this blood-vessel accident," Fletcher reported, "the patient had been restored from a dying condition to apparent convalescence." It was another pathetic case to lose.

From here on, however, the Oxford group began to click. They took a young woman whose vision was threatened by a horrible spreading ulcer and dropped penicillin into her eye hour after hour, saving her sight and possibly her life. They cured a terribly sick six-months-old baby, vomiting and feverish and shaken with convulsions, given up to die after sulfa-drugs failed to stop a kid-

ney infection. They saved a young boy dying from a staphylococcus infection of his blood stream and leg bones.

On August 16, 1941, Florey and his colleagues—all listed in alphabetical order—published the results on the first twelve patients under the title, "Further Observations on Penicillin." Their findings were unassailable: They had proved penicillin on human beings.

"I think the discovery and development of penicillin," said Florey, "may be looked on as quite one of the luckiest accidents that have occurred in medicine."

But there was still one huge hurdle to surmount. It had taken the Oxford workers more than two years to extract enough penicillin to treat twelve human beings, and there were patients by the tens of thousands whom it would unquestionably cure.

"We simply couldn't make enough of the stuff," one scientist declared. "We were being bombed, and most of our factories were all out to make things to hit the Germans. They couldn't give us sufficient aid."

Even before the report appeared in print, Florey called his shy assistant, Norman Heatley. "Pack up your things," he said. "We're going to America."

III

It is probable that sooner or later the Americans would have attempted to do something about this major problem of penicillin production. What made it much sooner was Hitler. When Florey and Heatley arrived in New York, five months before Pearl Harbor, they found that many Americans were already emotionally at war, already thinking about new war weapons and new drugs to save war wounded.

"We must have help on penicillin," the Oxford men started to explain. "We can't do it alone, and . . ."

"Will it help you win the war?" asked their American colleagues.

"Good Lord, yes!"

"Okay," said the Americans. "What do you want us to do?"

In Washington, the two Oxford men outlined their troubles at the Department of Agriculture, where they visited the mold specialist, Dr. Charles Thom.

"Go out to Peoria, Illinois," urged Thom. "We've got a big agricultural laboratory there. See Dr. Coghill. If anybody can help you grow molds, he's the man."

At the Rockefeller Institute in New York, René Dubos told them. "See Martin Dawson and his group here at Columbia University, and talk to the people at Mayo. They are already looking into penicillin."

Florey and Heatley flew to Peoria, arrived on a steaming hot day, and went in to see Bob Coghill, one of the top fermentation specialists in the country. They sat around his desk and quietly explained their needs.

"This penicillin sounds pretty tough," said Coghill.

"It is tough," said Heatley. "I've been working on it for two years, and I know it."

The American turned to Florey. "Could Dr. Heatley stay here for a while and show us everything he's learned?"

"Of course," agreed Florey. "You mean, then, that you'll consider starting the job for us?"

"We've just started," said Coghill.

Florey next went to the Mayo Clinic, where young Wallace Herrell and Dorothy Heilman were waiting for him. He talked to them and to their colleagues, checked the preliminary studies which they had made with some early American-produced penicillin, and left with them a small sample of the British product and a tremendous dose of enthusiasm. Everywhere that Florey visited, he left behind this burning enthusiasm. Modest and retiring, he was the complete antithesis to a high-powered salesman, but few Americans could resist him. He went from Mayo back to Washington, sold the newly organized Committee for Medical Research, and won a powerful ally in Dr. A. N. Richards, CMR chairman.

He sold other scientists in Washington, in New York and in Boston. But above all, he sold America's great drug industries.

"We need additional research on penicillin," he told one drug manufacturer. "We need more tests on penicillin. But primarily, we need production—we need penicillin!"

The manufacturer grinned. "Hell, Dr. Florey, you're in the United States now. Production? Why, that's our middle name!" And, one by one, America's great drug manufacturers moved in on the job.

It was the fall of 1941 when America's production specialists—chemists and bacteriologists and engineers—went to work on penicillin. How much did they need? Nobody knew exactly, but somebody suggested at least two pounds as a minimum for test purposes.

"Two pounds?" groaned Coghill. "It's too stupendous!"

How much might the job cost? Nobody knew that, either. If they had realized then that eventually America and England together would gamble nearly a hundred million dollars, they might never have started. All that anyone knew was that penicillin—penicillin by the millions and millions of units—might save a lot of lives.

For nearly a year the production crews sweated and strained. They built great vats to grow mold; they tried scores and scores of different mold foods; they developed dozens of methods to extract the penicillin, to purify it, and to concentrate it. Thinking that they might find a more productive strain of mold lurking somewhere in the soil, the "mold merchants" at Peoria asked the Army Air Forces to bring back a sample of soil from every airfield in the world. They tested every strain of mold that appeared on old bread, old leather, and old cheese. But during that first year the amount of penicillin they produced was pitiful, and all during that year civilian and military doctors pleaded for supplies.

Everything conspired to build up that demand. Florey's first reports had opened the eyes of every British doctor, and the British army, the navy, and the RAF put in immediate requisitions. Civilian doctors called for penicillin to treat victims of Nazi bombs.

Even Alexander Fleming, still at St. Mary's Hospital in London, asked for a supply.

He called Florey at Oxford one day and said, "We've got a man here with a streptococcus meningitis. Sulfa-drugs don't do him a bit of good. We started oxygen last night, but he's dying. Do you have any spare penicillin?"

"Not very much," Florey answered. "I'll send you what we can."

Fleming got his penicillin, injected it directly into the delicate lining of the spinal cord—the first time anyone had tried this with penicillin—and saved his patient's life. "Recovery was uninterrupted," he reported to Florey.

Fleming got a little bit of penicillin. Most doctors didn't, not in England nor in America, where another dramatic report—use of penicillin on victims of Boston's Cocoanut Grove fire—heightened the demand.

In 1943, however, things began happening on the production front. At Peoria, Coghill and his men found two superior strains of mold; one had been there all the time in the laboratory's mold collection, and the other was found growing peacefully on a cantaloupe in a Peoria fruit market. Also, for no apparent reason, they took some corn-steep liquor—the fluid left over when corn is soaked in water during the manufacture of starch—and added it to the regular mold food; to their amazement, it increased penicillin yield by ten times.

Production in January of 1943 was low—one hundred million units of penicillin, about two ounces, enough to treat perhaps a hundred and fifty men. By May, the monthly output was up to four hundred and twenty-five million, by July it reached seven hundred and sixty-two million, and the "mold merchants" were beginning to hope that maybe they could meet the demand—but the demand went up, too.

British doctors, including Dr. Ethel Florey, reported additional hundreds of successful case histories—men, women, and children treated in civilian hospitals. Military doctors added more penicillin triumphs. Florey himself had spent the summer months in Algeria,

testing penicillin on wounded men evacuated from the Battle of Sicily, with the temperature over ninety, clouds of dust from every passing vehicle sweeping over the cots, and swarms of flies settling on every exposed wound; even under these conditions, he announced, and even in the treatment of deadly brain infections, the action of penicillin was remarkable.

In August of 1943, American production climbed to nine hundred and six million units.

That month, Dr. Chester S. Keefer of Boston reported the results of twenty-two American teams who had tested penicillin on five hundred closely watched patients. The results: three hundred and sixty-six recovered or improved, forty no effect, ninety-four deaths. It was the first major test of the drug in the United States. Keefer was the one man given the responsibility for deciding which patient should get penicillin and which should not. Deluged by a nationwide flood of pathetic requests from doctors and patients, he permitted the drug to be used only where it would add to medical knowledge. Time after time he was forced to turn down frantic pleas to save the lives of his friends and his friends' children.

It was also that month that Dr. Leo Loewe and his associates at the Jewish Hospital in Brooklyn succeeded for the first time in stopping one of the most devilish of all infections. This was subacute bacterial endocarditis, a bacterial infection of the heart valves, with a well-established mortality rate of 97 per cent. With penicillin, they reduced the rate to less than 20 per cent!

In September of 1943, production jumped to a billion seven hundred eighty-seven million units—two full pounds of penicillin, but that original goal had long since been expanded. American workers were now using penicillin to treat gonorrhea—reporting complete cures sometimes in forty-five hours—and there was a lot of gonorrhea to be cured!

In October, John Mahoney and his men from the U.S. Public Health laboratories on Staten Island made the most exciting American contribution to the medical knowledge of penicillin. For years, seeking a better treatment for syphilis, they had routinely tried

every new drug that appeared on the market. There was no reason why penicillin might have been expected to work, for the microbe of syphilis is no relative of the staphylococci or the streptococci or the pneumococci. But they tried penicillin anyhow, and penicillin *did* work!

Now the demand reached new peaks, but now the production men—the Peoria "mold merchants" and their industrial colleagues —were going high, wide, and handsome. Their huge vats, ten- and fifteen-thousand-gallon tanks, were pouring out penicillin. By the end of the war, they were making a trillion units—more than a thousand pounds—a month. The battle of penicillin production had been won.

IV

To a number of research workers, the development of penicillin was splendid, wonderful, magnificent, but it was not in the least surprising; they had long suspected the existence of such an admirable substance.

Among them was dark, slouching René Jules Dubos, the sparkling French microbiologist of the Rockefeller Institute for Medical Research. Born in 1901, he entered the National Institute of Agronomy in Paris at the age of eighteen, graduated two years later, and got a job as an assistant editor of an agricultural magazine in Rome. It was not a particularly satisfying job, and Dubos became increasingly bored with editing articles about the scientific researches of others. He wanted to do some research of his own.

In 1924 he got his chance. The world's great soil experts held an international congress in Rome, and the Frenchman managed to meet Dr. Jacob Lipman, director of the New Jersey Agricultural Experiment Station.

"I would like to go to America and continue my studies," Dubos said. "I have read about your work in New Jersey. Could you possibly find room for me?"

"Yes," Lipman answered. "I think we might. But tell me about your own work. What do you want to do?"

Dubos told him, enthusiastically describing his plans to investigate the microbes that live in every clump of soil.

"All right, come ahead," Lipman decided. "We'll try to line up a fellowship for you."

That fall, Dubos arrived in the United States and went to Lipman's laboratory at New Brunswick, New Jersey, where he learned that no fellowship would be available for a good many months.

"It is unfortunate but not disastrous," he said. "I can do other things."

Until the fellowship was finally granted, Dubos did a great many other things to keep eating. He helped in the laboratory, washed bottles, prepared solutions, and translated scientific papers. Meanwhile he started working for his doctor's degree at Rutgers University and he began his research under Lipman.

Actually, Dubos was not under Lipman's immediate direction. His supervisor was an earlier Lipman protégé, thirty-six-year-old Selman Waksman, a Russian-born microbiologist who had come to America in 1910, studied at Rutgers and the University of California, and then gone back to New Jersey to study microbes in the soil. This combination—the colorful, imaginative Frenchman and the painstaking, wise, little Russian—was destined to become one of the great pioneering teams in the history of microbe fighting. It made no difference that Dubos soon moved to New York to join the Rockefeller staff; these two men were together in opening a new world to conquest—the world of the soil.

"In the soil," they said, "there are thousands and thousands of different kinds of microbes. These are the normal soil microbes, and almost all of them are harmless to men and animals. What, then, has become of all the bacteria causing typhoid, dysentery, cholera, diphtheria, pneumonia, bubonic plague, tuberculosis, leprosy, and numerous others? These do not survive long in the soil."

Take a spoonful of soil and you practically never find these disease germs. In fact, if you add real disease germs to the soil, they soon are destroyed or overwhelmed, and they disappear.

"What is there in the soil," these two men wondered, "that gets rid of most disease germs?"

There was one obvious possibility. Among the many harmless soil microbes, there might be some which can attack, destroy, and digest any harmful germ which comes their way.

In the late 1920's, Waksman and Dubos began looking for them. They realized at the outset that it would take a thousand human lifetimes to look through soil, pick out each of the thousands of kinds of normal soil bacteria, and then test each in turn against deadly germs; instead they turned to two simple short cuts.

Dubos selected a method of elimination by starvation.

"These soil microbes have to eat," he reasoned. "We shall give them a diet of pure pneumonia germs, day after day. The microbes that cannot digest pneumonia germs—they will starve to death. The microbes that can eat them—they will survive. And they might be very useful!"

He went out and got samples of soil from swamps, forests, farms, gardens, and vacant lots. He baked each sample just enough to destroy the available food without killing the soil microbes. And then he gave the soil microbes their sole item of food—pneumonia germs. In the spring of 1938, after years of work, he opened his bottles and looked for any survivors. What he found was a tiny, rod-shaped bacillus with a voracious appetite for pneumonia germs.

From this harmless microbe, he extracted a mixture of chemicals which enabled it to digest the bodies of pneumococci. This mixture is known today as *tyrothricin.* In a test tube, it can digest pneumococci with the greatest of relish, and it can also digest staphylococci and streptococci. But Dubos didn't want merely to kill these germs in a test tube; he wanted to destroy them in sick and dying patients.

The first animal tests were discouraging. He tried tyrothricin

on mice infected with superlethal doses of virulent pneumonia germs, and found that this stuff killed the germs. It was a sure cure for pneumonia—except that it wrecked the animals, too, by dissolving their red blood cells.

"Don't let that worry you," said the physicians. "We won't inject your tyrothricin into the blood stream. We'll apply it locally."

They soon showed that tyrothricin could be used safely and effectively in the local treatment of ulcers, infected sinuses, impetigo, and other skin infections.

Two years after Dubos turned up tyrothricin, Waksman and his New Jersey colleagues came out with another germ-dissolving chemical which they called *actinomycin.* They had found it being secreted by a soil mold which grew on plates of germs and, like penicillin, dissolved any germs in the vicinity. Actinomycin was murder against germs. Diluted one hundred million times, it could stop bacterial growth. It was active against almost every bug which causes human disease, even more active than penicillin. But it was also about six times deadlier than cyanide to human beings. Actinomycin was definitely not suited to medical use.

A year later, while Howard Florey and his group were treating the first Oxford patients with penicillin, Waksman picked up a lovely lavender mold which secreted *streptothricin.* This was a little safer; it killed experimental animals, but only after a week's delay.

Finally, in 1944, the New Jersey group—Waksman, Albert Schatz, and Betty Bugie—took a gray soil mold, *Streptomyces griseus,* and isolated *streptomycin.* This was really something. Not as safe as penicillin, it could work magic that not even penicillin could perform. Physicians quickly reported that it could destroy the germs which cause tularemia or rabbit fever, mastoid infections, influenzal meningitis, many infections of the kidney and bladder, certain types of tuberculosis, brucellosis, and bubonic and pneumonic plague.

No sooner had the big American drug manufacturers licked the job of penicillin production than they were asked to take on strep-

tomycin production. This new task was even more difficult. "Penicillin was bad enough," exclaimed one experienced manufacturer, "but this streptomycin is simply awful!"

Nevertheless, they licked this problem, too.

By the end of World War II, research men all over the world were reporting more and more germ-killers which they had isolated from molds, yeast, fungi, bacteria, lichens, mosses, lilies, buttercups, tomatoes, honeysuckle, and seaweed. To all of these substances—found first in nature and, in some cases, synthesized later by chemists—Waksman applied the name of "antibiotics."

In 1944 Alexander Fleming and Howard Florey were knighted by King George VI for their work on penicillin. In 1945 they shared with Ernst Chain in the Nobel prize for medicine.

"This prize," they were told, "is for a vital job well done."

Fleming disagreed. The job, he indicated, had only been barely started. "There are thousands of microorganisms which manufacture complicated substances," he said. "Some of these may be better than penicillin. . . . It would be strange indeed if the first one described remained the best."

CHAPTER XII

The Devil-Slayers

LOCOCK TO LENNOX, AND THE DRUGS AGAINST EPILEPSY *

TODAY in the United States, epilepsy is more prevalent than active tuberculosis or diabetes. Its victims number more than five hundred thousand, perhaps nearly a million. It is difficult to tell; for until a few years ago, each of these victims was doubly cursed—once with the disease and once with the shame of the disease.

That double curse has existed for scores of centuries, for epilepsy is one of man's oldest diseases, perhaps older than man himself. But now epilepsy can be controlled—because of an Englishman who was lucky, a German who tried everything, and an American who refused to quit.

The cave man knew epilepsy and blamed it on a demon, a devil which might be induced to depart if a hole were bored in the skull of the victim and the proper incantations said. The early Greeks knew epilepsy, but their medicine men explained it as a visitation of a god. If the victim ground his teeth or acted like a goat, they said, the responsible divinity was Cybele, mother of the gods; if he cried out in sharp, shrill tones like a horse, then unquestionably Poseidon had taken possession; and if the unfortunate foamed at the mouth or struck the floor with his feet, it was clearly the work of the war god Mars. The early Greek doctors gave the "falling sickness" its first formal name. They called it the Sacred Disease, and prescribed prayer and offerings and sacrifice.

Twenty-five centuries ago, the great Hippocrates dared to challenge the role of the gods. He wrote:

"It is thus with regard to the disease called Sacred: it appears to me to be nowise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other affections."

Those who attributed it to the gods, he said, were "conjurors, purificators, mountebanks and charlatans . . . who give themselves out for being excessively religious, and as knowing more than other people."

Hippocrates left with his students a description of an epileptic seizure which is still valid today. "The patient loses his speech, and chokes, and foam issues by the mouth, the teeth are fixed, the hands are contracted, the eyes distorted, he becomes insensible, and in some cases the bowels are evacuated. And these symptoms occur sometimes on the left side, sometimes on the right, and sometimes on both."

He recognized particularly the mortifying shame that engulfs the victim.

"Such persons as are habituated to the disease," he explained, "know beforehand when they are about to be seized, and flee from men; if their own house be at hand, they run home, but if not, to a deserted place. . . . This they do from shame of the affection. . . . And little children at first fall down wherever they may happen to be, from inexperience. . . ."

For the next two thousand years, hardly a single important addition was made to the knowledge of the disease. The Arabs gave it the name *epilepsy* from the Greek word which means *to seize,* or *falling upon.* The famous physician Galen presented various prescriptions for epilepsy, and blithely convinced himself that if his remedies failed in even one case, it was due entirely to the obvious stupidity of the patient. Later, certain saints were selected as the protectors of epileptics, and victims were considered to be the special charges of St. John the Baptist, St. Vitus, St. Cornelius, St.

Valentine, St. Gilles, St. Hubert, and St. Michael, the particular foe of Satan. But, so far as the patients were concerned, prayers to Christian saints seemed to be no more effective than the sacrificial offering to Greek gods, incantations to pagan demons, or the self-assurance of medical men.

In the seventeenth century, with the birth of modern anatomy and surgery, doctors began to use their eyes instead of their philosophies to seek an explanation for epilepsy. They found no simple explanation, but they did uncover clues which pointed undeniably to the brain. And at the same time, they began an intensive but fruitless search for an effective cure.

Earlier physicians had tried and often praised such remedies as powdered human skull, the fresh blood of a dying Christian gladiator, elk's claw, wolf's liver, the gall of a boar fried with urine, and the stones of swallows. Now these more modern workers turned to opium, hashish, belladonna, turpentine, acids, caustic alkalis, and mistletoe.

The English herbalist Parkinson tried a concoction of digitalis and reported: "It hath beene of later experience found also to be effectual against the Falling-sicknesse, that divers have beene cured thereby; for after the taking of the decoction of two handfulls thereof . . . they that have been troubled with that disease 26 yeares, and have fallen once in a weeke or two or three times in a moneth, have not fallen in 14 or 15 moneths, that is until the writing hereof, which I thinke may be said to be an absolute cure. . . ."

But in spite of such enthusiasm, digitalis was no absolute cure, nor even a minor one, for epilepsy. And neither were gladiator's blood, belladonna, mistletoe, or the hundreds of other drugs. By the early 1800's, most doctors had reached the unhappy conclusion that the control of epilepsy was hopeless. They had tried every conceivable, reasonable, intelligent, rational approach, and found nothing. All they could do was select the proper words of sympathy to extend to the saddened relatives.

It was time for an irrational accident.

II

Even his best friends agreed that in all his life, Sir Charles Locock had only two ideas. One was that the art of medicine, properly practiced, might be an excellent way to wealth. This one was right; Locock became one of the wealthiest society doctors of his times, and the outstanding obstetrician in London. He was also a short, pugnacious bantam, a hypocrite, an egotist, and a mid-Victorian snob, and his bedside manner was magnificent.

He was born in 1799 in Northampton and, at the age of twenty-two, graduated from medical school at Edinburgh. Soon afterward he moved to London and started the practice of obstetrics in the General Lying-in Hospital in Lambeth. In certain medical circles, it was commonly accepted that at this hospital even a moderately good obstetrician could depend on building up a large and lucrative private practice for himself. Locock was better than moderately good, and the practice he quickly developed in fashionable society was termed no less than remarkable.

At the age of twenty-seven, he courted and won Miss Amelia Lewis, described as "a lady of large means." She gave him a fortune and, over the next eleven years, five sons.

Locock did not retire to live on his wife's wealth. He worked hard, took excellent care of his pregnant patients, insulted their husbands, sent enormous bills, was rude to his less successful colleagues, and consumed enormous quantities of snuff. To a small group of intimates, he could be a charming, amusing companion, lighthearted and genial, a vivid talker, and an excellent storyteller. His racy anecdotes, told in many an exclusive London club, were so famous that they were mentioned in his obituary.

In 1839 he was accorded the highest honor that could be paid to any English obstetrician. He was named physician-accoucheur to Queen Victoria, a title which he held until his death. He was present at the birth of all nine of her children, he induced her to become one of the first women to use chloroform during childbirth—he helped administer the anesthetic—and, most surprising

to his colleagues, he and the Queen became the warmest and closest of friends.

For the next fifteen years, his position in British medicine was unassailable. A young duke or earl or heiress was not to be considered properly born unless Dr. Locock had a hand in the delivery. He was elected to almost every important medical society. London quacks cashed in on his popularity by flooding the market with patent medicines labeled "Locock's Pulmonic Wafers," or "Locock's Cough Lozenges." The Queen made him a baronet.

While his popularity as an obstetrician was unparalleled, his reputation as a teacher and scientist was nonexistent. He taught obstetrics for a short while, and was remembered not for any inspiring lectures but for the manner in which he stamped out a classroom rebellion. He was not interested in science or in research. He was not credited with making a single improvement in his own field of obstetrics, and he published only three medical works—three short articles for a medical cyclopedia, none of them based on original work.

In March, 1856, however, he had his second great idea—and one which was quite wrong.

During that month, he was visited by the distressed father and mother of a charming, attractive young woman who had suffered from epilepsy for nine years. A normal life, marriage, and a place in society were all impossible for her.

"But there is nothing I can do," Locock told her parents. "You must understand that this matter of treating convulsions is quite out of my field. I am sure that if you would consult other physicians . . ."

"Oh, we have, doctor!" said the mother. "We have consulted everyone, everyone."

"In that case, you see that there is nothing I can suggest or that . . ."

Here the father interrupted. "But, I say, Locock—isn't there anything new, any new treatment that has been found?"

"Nothing," Locock answered. "I can assure you that I am quite

diligent in reading all the medical journals. I read not only the British reports, but also the French journals and the German . . ." He broke off suddenly, tapped his fingers together for a moment, and then reached for his ever-present snuffbox.

"Hm-m," he continued. "I think there may possibly be something new. Something quite new. I should like to see your daughter again in—shall we say two or three days? There is a special material I shall need to obtain."

The material was potassium bromide.

Bromine, the active ingredient of the compound, had been known to science only since 1826, when it was discovered in Mediterranean sea water by a young French pharmacist. In 1835 bromine—in the form of potassium bromide—was accepted by the British medical profession for the treatment of enlargement of the spleen, but in 1851 it was thrown out as totally useless.

A few years later, a German investigator obtained some bromide and reported a most remarkable observation. He took the bromide for several days and noted that he had become sexually impotent; when he stopped taking the chemical, his potency returned. The astonished German repeated the test and got the same effects. Next he induced some of his colleagues to try the bromide, and they, too, underwent this quite startling change. Then he wrote a little scientific report and sent it to a journal for publication.

It was this report which, somehow or other, had come to Locock's attention and which had started him thinking.

"There are some people who claim epilepsy is due to sexual indulgence," he thought. "Don't see how that could be. But maybe it is. And, by George, in women—why, many epileptic women get convulsions about the time of their menstruation. Maybe sex *is* at the bottom of epilepsy!"

And if sex—sexual indulgence or sexual strain—were tied up with epilepsy, then the best treatment in the world would be something which dampens sex. Something like potassium bromide!

"Go to the chemist," Locock told his assistant, "and have him get me some potassium bromide—about a hundred grains of it."

More than a year went by. On the night of May 11, 1857, Locock dined at his club and at eight o'clock went to the regular meeting of the Royal Medical and Chirurgical Society of London. It promised to be a boring meeting, but Locock had to be there since he was president. At the appointed hour, he rapped the gavel on his table, asked for the usual reading of the minutes—which were duly approved—and then called on the first speaker.

"We shall hear from Dr. Sieveking," he announced, "who will address us on the subject of" —he fumbled through his notes—"subject of—ah, quite so—a report on fifty-two cases of epilepsy."

Dr. Edward H. Sieveking, the distinguished physician of St. Mary's Hospital, commenced his report. "I venture to express a feeling of skepticism with regard to the positive certainty of any cure of epilepsy," he began.

He embroidered on this theme at some length. He described his fifty-two patients, and the treatments he had prescribed for them. Nothing, it appeared, was of noticeable value. The only suggestion he could produce was to "remove local irritation by counter-irritation" and "promote the healthy action of the secernent organs, and give a tone to the constitution by vegetable and metallic roborants." Lest any of the audience might become even slightly optimistic, however, Dr. Sieveking concluded: "I believe there is no specific cure for epilepsy."

There was a perfunctory spattering of applause. Dr. Locock asked if there were any discussion. There being none, he called for the next paper, which was presented by a Dr. Webster, who likewise had no cure to suggest but offered to comment on causes.

"Fright," he observed, "is a very common cause, especially in young and hysterical females. Only recently, I heard of a young lady who got fits after paying a visit to the Chamber of Horrors in Madame Tussaud's wax museum. . . ."

There was no discussion from the floor, and the program continued with a Dr. Stewart, who reported that he had tested numerous remedies for epilepsy, all without success. "In despair, after trying everything else," he reported, "I tried the internal and ex-

ternal application of a combination of nitric and hydrochloric acids." And not even this hellish mixture worked.

At the end, Dr. Locock rose to his feet. "These very significant contributions," he said, "are now open for any general comments from the members."

There were no comments.

"Or questions."

There were no questions.

"Dull program tonight," Locock murmured to his secretary. "Perhaps I should say something myself." He cleared his throat and turned to the audience.

"It has just come to my mind," he said, "that there is another form of epilepsy to which special notice has not been drawn tonight. A type confined to women. Observes a regularity of return which seems to be connected with menstruation."

And then he remarked, in a very footnote-ish manner, that within the last twelve months he had been led to try a new remedy. "It has so far answered my expectation that I think it desirable that it should have a larger trial. It should be made known to a larger number of persons."

In a few words, he reviewed the German experiment and the observation that bromides can produce a temporary sexual impotency. He described his epileptic patient—the young woman who had been taken from doctor to doctor without getting any help—and mentioned that she had been suffering at least two major epileptic attacks every month.

"After the administration of potassium bromide," he said, "the results have been that she has not had another attack. I have also tried the remedy in fourteen or fifteen other cases. It has failed in only one."

Thus, in these mild sentences, the bromides were introduced for the treatment of epilepsy.

Locock never drafted a formal report on his work, never gave a lecture on the subject. His contribution consists entirely of those brief phrases, presented as an impromptu comment. He declined

to expand a dozen or so tests, leaving that task to Hughlings Jackson in England and the remarkable Brown-Séquard in France, who came along later and rescued the bromides after Locock's own colleagues tried them halfheartedly and then ignored them.

Another who aided in the campaign for potassium bromide was Sir William Wilks, who said, "In books, bromide was recommended amongst other remedies, but was condemned as worthless. I tried it and witnessed results more remarkable than I had ever anticipated."

It is not of great importance today that the obstetrician and drug-hunter-by-accident neglected to exploit his discovery. Others popularized the bromide treatment so widely that in the year 1899 one London hospital—the National Hospital for the Paralyzed and Epileptic—dispensed almost four thousand pounds of bromides, the equivalent of nearly fifteen hundred doses a day.

Nor is it of great importance today that Locock's inspired reasoning was wrong. The bromides worked in epilepsy not because they dampened sexual ardor but because they acted as sedatives on a particular portion of the brain.

What is important is that their discovery showed for the first time that the demons of epilepsy can be attacked by drugs. The bromides ended two thousand years of utter hopelessness.

III

The bromides were good, but they were far from perfect, helping only a small proportion of epileptics—perhaps twenty out of a hundred. There was a desperate need for something better.

One day in the little city of Gleiwitz, in Upper Silesia, a group of children went off for a picnic. They found a comfortable spot near a stream and began to unpack their baskets of bread and cheese and fruit. Suddenly a girl uttered a shrill scream and fell to the ground in terrifying convulsions. Young Alfred Hauptmann, son of the city physician, was one of the children who witnessed that sight; he never forgot it.

When Hauptmann finished his schooling at Gleiwitz and Frankfort-am-Main, he studied medicine at Heidelberg and Munich, and finally moved to the University of Freiburg, where he became a resident in the psychiatric clinic. There he worked with schizophrenics and manic depressives, with idiots and men with battered skulls, with victims of creeping paralysis, and with victims of epilepsy. To these last patients, he administered bromides which sometimes helped but more often did not.

"Bromide is a sedative," he reasoned. "Now, if I could only get a drug which is a better sedative, a drug which would really reach the sleeping centers in the brain . . ."

There were plenty of sedatives, the old reliables like chloral and the new barbitals like veronal which were now beginning to stream out of German drug laboratories.

"They all make you sleep," he told Professor Hoche, his chief, "yet none of them stops convulsions. But someday there will be one . . ."

Month after month, he tested each new barbital as it came on the market. He pestered the laboratory men, asking for experimental drugs which they might make. Dozens and dozens of these compounds were sent to his wards, but not one of them had any value. Finally, in February, 1911, when Hauptmann was thirty, the long-awaited drug came along. It was new, relatively untested, aimed primarily at overcoming insomnia; it was phenobarbital, soon to be known more widely under the trade name of luminal.

Hauptmann selected a few patients who were victims of the most severe epileptic convulsions, whose attacks came so frequently that they had to be kept in the hospital, and who could get no relief with bromides. Within a few weeks, he realized that phenobarbital was helping these patients. A year later, after tests on some thirty of them, he reported his findings.

"Phenobarbital," he wrote, "tends to exert a favorable influence on epilepsy by reducing the number and severity of the attacks. Its field of applicability will be chiefly in those very severe cases of

epilepsy which can no longer be controlled by the largest dose of bromides."

The German doctor was strangely cautious in his conclusions. "At the time," he said later, "nobody else was particularly excited about it. And although I was still very much interested in epilepsy, I was also interested in a very flashy automobile which I was buying on a monthly installment plan."

Although few European doctors seemed to be impressed by his announcement, some Americans were quick to apply it. One of them was Dr. Julius Grinker of Chicago, who happened to read Hauptmann's article in a German magazine and immediately administered phenobarbital to one of his patients, the thirteen-year-old son of a clergyman. This youth had been suffering five or six attacks a day, and bromides had done nothing for him except produce an irritating skin rash.

"I decided to try phenobarbital," Grinker declared. "The effect was marvelous and almost instantaneous. No more attacks were reported."

Partly because of World War I, Grinker didn't get around to writing his report until 1920. Then it served to give phenobarbital an enthusiastic send-off, and within a few months the drug was in wide use in both America and Europe. Phenobarbital was good, too; it was more effective than bromides, it helped more epileptics, and it did not produce the so-called bromide rash. But it was not perfect, either, for it could help only about forty out of a hundred epileptics, and—after all, phenobarbital *is* a barbital—it often produced drowsiness and a feeling of stupor. Most victims, however, preferred stupor to convulsions.

And now the devils of epilepsy were weakening, for there were two drugs against them—bromides and phenobarbital.

IV

In 1920, the year that American doctors rescued phenobarbital from impending oblivion, a worried, tired medical missionary re-

turned from China to the United States to open an unprecedented campaign against the falling sickness and against a good many of his medical colleagues.

He was Dr. William Gordon Lennox, son of a Colorado gold-mine operator who had struck it moderately rich in the Cripple Creek gold rush and then had taken his money and invested it in a two-hundred-thousand-acre cattle ranch in Texas. Young Bill Lennox did not want to run a cattle ranch, and so, after he graduated from Colorado College and married Emma Buchtel, daughter of the governor of Colorado, he went to Harvard Medical School. When he completed his studies at Harvard and finished his internship at Massachusetts General Hospital, he announced that he was leaving for China.

One of his professors thought it was an excellent step. "You need a vacation, Lennox. The trip will do you good."

"But it's no vacation, sir. I'm going to stay out there."

The professor was startled. "Stay there? Good heavens, man, why?"

"I'm going to be a missionary. I'd like to be as helpful as I can, and there's a great need for missionaries in China."

"But you're a medical man. You'll be wasting your talents."

"I don't think I will. There's an even greater need for medical missionaries."

In 1916 Lennox, his wife, and their two baby daughters, Mary Belle and Margaret, sailed for the Orient. They went to Peiping, where he started work at the Methodist mission. There he learned to speak Chinese, he introduced the latest newfangled medical and surgical tricks to his oriental and occidental colleagues, and he saved bodies and—where possible—souls. Mrs. Lennox, whose father had been a Methodist missionary in Bulgaria before he became a governor in Colorado, worked closely with him, helping those who were sick in flesh or spirit.

After four years in China, Dr. Lennox discovered epilepsy. The promising child of his best friend developed convulsions and

neither the most skillful Chinese doctors nor the outstanding American medical men in Peiping could help. At the same time, the two Lennox children became ill with dysentery, and one of them was desperately sick. The great Professor Billings, passing through Peiping on a mission to Russia, examined the girls and said, "Take them home. China is not for you."

So Lennox left his mission and the splendid Rockefeller medical school, to which he had been loaned, and took his family back to America. Then he went to Harvard to look for sick people who needed medical and social help as sorely as had the Chinese, and at the same time he looked for something to aid his friend's epileptic child. In Boston, he thought, there would surely be specialists who could provide this aid, but the doctors in Boston were no better than the medical men in China.

"Epilepsy?" said one. "Here is a prescription for bromides. To be taken three times a day. No school. Better have the child put on a farm."

"Epilepsy?" said another. "I'll give you a prescription for bromides. Teaspoonful in water with each meal. Have the parents considered sending the child to an epileptic colony?"

"Epilepsy?" said a third. "Too bad. No meat, no excitement. Give bromides."

Lennox, distressed with such advice, felt sure there must be more knowledge somewhere, and he turned to the medical library. The most up-to-date book, however, was fifteen years old, and the newest medical journals contained only ridiculous essays on the influence of enlarged colons and on some mysterious "epilepsy bacteria." The most authoritative experts agreed that epilepsy is "by definition a progressive disease, ending in mental and physical decay, completely hopeless."

Week by week, the convulsions of the child continued and a slow anger grew in the kindly missionary. "Nowhere," he declared, "could I find any evidence of a careful search for causes or new treatments." Gradually, he came to the realization that, poorly pre-

pared though he was for research, he himself would have to attack this hopeless problem which was shunned by the well-prepared experts.

He went to see his schoolmate and friend, Stanley Cobb, the handsome, brilliant doctor who was already on his way to becoming one of America's greatest nerve specialists. Cobb needed no persuasion to study epilepsy, for he had long been thinking of that problem. They talked excitedly of experiments which might be performed, of treatments which might be investigated, of old legendary drugs which might be re-examined, of questions which eventually must be answered. Then came an immediate question: "What will we do about money?"

Without funds to support the research, it was impossible even to begin work. But providence took a hand. In New York, the epileptic son of a wealthy lawyer had obtained what seemed to be miraculous help from two weeks of semi-starvation. The lawyer went to the Rockefeller Foundation.

"Who can best find out why starvation helped my son but did not cure him?" he asked.

Back came the answer, "Stanley Cobb."

With the backing from the lawyer, the money-begging Harvard Epilepsy Commission was organized, and Cobb and Lennox were on their way.

Draft-board reports just coming in from World War I showed that five persons in a thousand—about six hundred thousand in the United States—were victims of epilepsy. Only a small percentage of them could be helped by bromide or by phenobarbital, which was just being pushed to the fore.

"I can't believe that all knowledge died with Locock and Hauptmann," insisted Lennox. "We might be able to do better."

The work therefore began with a study of starvation—which was quickly found to be no cure—and then went on through special diets, blood chemistry, mental treatment, the actions of all the time-honored (but useless) drugs like mistletoe and morphine and

hashish, and the effects of some new, secret, and highly expensive remedies.

"These secret remedies turned out almost invariably to be nothing but bromide or phenobarbital, with a fancy name and a fancier price," the doctors reported.

"It is remarkable," they added later, "how many tons of drugs have gone down the gullets of epileptics—and with such little benefit."

In 1928, after years of ceaseless investigation, of reading and rereading all the books and reports from Hippocrates to Hauptmann, and of conferences and discussions, they wrote a report of their findings. It was, at least in one respect, a remarkable volume, for it showed that the "knowledge" of epilepsy was a monument of questionable ideas based on a flimsy foundation of fact.

"After two thousand years of studying epilepsy," Lennox stated, "the medical profession was stranded in a maze of blind alleys."

It seemed that the direct cause of an epileptic attack is some peculiar chemical or physicochemical change in the nerve cells in the brain, and that this change makes certain clumps of cells discharge at "an abnormal and functionally devastating rate." But what produces this change in the nerve cells? What can you do to prevent it? What can you do to overcome it? And isn't there something better than bromides or phenobarbital?

"There must be something better," Lennox insisted, and he went back to find answers to all the questions that were now clearly outlined. Other doctors told him he was wasting his time, that he could hardly hope to succeed where his predecessors for twenty centuries had almost uniformly failed. Some of his colleagues pointedly observed that Lennox himself was not likely to make any real discoveries, for he was really not a properly trained research man. Politely, the Colorado missionary admitted his lack of special laboratory experience but continued to train himself, and—also politely—continued to fight against this pervading blanket of hopelessness.

He was almost demure in his attitude, always modest and gracious, but he would yield to no one in his fight for the epileptics. "Patients with convulsions," he would remark quietly, "suffer because the medical profession itself suffers from an attitude of hereditary mental defeatism."

For the next half dozen years, Lennox—affectionately dubbed "Cowboy Bill"—pushed on, working almost alone. He made careful measurements of epileptic patients, studying the reactions of their nerves, the chemical composition of their blood and spinal fluid, and the weights of their brains, livers, hearts, spleens, and kidneys. He became an amateur genealogist to trace the history of epilepsy in families and to understand the heredity of the disease. He quietly accepted the rebuffs from some of his colleagues but continued to preach epilepsy, to sell epilepsy, to call for more money for epilepsy, to get more laboratories for epilepsy, and, above all, to interest more men—more younger men—in doing research on epilepsy.

In the early 1930's, a brilliant young brain specialist, Dr. Tracy J. Putnam, fell under Lennox's spell. Putnam was no missionary; he was a handsome, well-dressed, suave Harvard expert, a keen research man, a skillful surgeon, and a one-time assistant to Harvard's world-famous brain surgeon, Harvey Cushing. He was practically everything that Lennox was not, but Lennox made him a convert.

"At first," Putnam said, "it looked completely hopeless. Nothing but blind alleys. The boys had tried diet, surgery, drugs, everything they could think of. Everything came out with negative results. Nothing was any good—nothing but bromide or phenobarbital. I was ready to quit before I started. But Bill Lennox wouldn't let me."

The one thing that Lennox kept emphasizing was phenobarbital. "Why is it even partially effective?" he asked. "Why does it work?"

Putnam didn't know. Phenobarbital, he realized, was not a particularly mysterious chemical. It was one of the barbital family, but, strangely enough, the only member of that family which

worked against epilepsy. Methyl-barbital, ethyl-barbital, di-ethyl-barbital, all the rest of the barbitals—they could put you to sleep, but not one of them could prevent convulsions.

"You could hammer your brains out trying to figure what it all meant," he said, "but you couldn't get beyond that one fact—the only barbital for epilepsy was phenobarbital."

What, then, is so marvelous about phenobarbital? And what is this phenobarbital?—nothing but a combination of phenol with barbituric acid. There was no reason in the world why phenol, alias carbolic acid, should help epileptics, so it must be the barbituric acid which worked.

"But, damn it all," he muttered, "barbituric acid *doesn't* work—not unless it's coupled with phenol!"

And then he came out with a completely astounding idea. "Maybe everybody is wrong," he thought. "Maybe it is the phenol which does the work!"

This possibility seemed so hopelessly remote that, for many months, Putnam put it aside. Then he went to Nashville for a lecture and had dinner with his friend Tinsley Harrison of the University of Tennessee. Somewhere between the roast beef and the coffee, they began talking about uremia, the dangerous situation in which the kidneys fail to excrete uric acid. When too much uric acid remains in the body, the patient goes into convulsions.

"The odd thing about it," remarked Dr. Harrison, "is that these convulsions seem to be prevented if there are phenol compounds in the blood. . . ."

Here it was again, phenol and convulsions—or, rather, phenol and *no* convulsions!

Putnam went back to Boston and one night—it was the fall of 1935—he sat at his desk, ran through the catalogues from all the American drug manufacturers, and listed every phenol derivative on the market. From this list he scratched off the names of compounds which he knew would be toxic. He put in an order for all the rest.

Somewhere in that list—a long list of phenol-this, di-phenyl-that,

and tri-phenyl-the-other—might be the name of the magic drug to control epilepsy.

The first batch of chemicals to arrive in Putnam's office happened to come from Parke, Davis and Company in Detroit. In the bundle were not only the compounds he had ordered but also some others thrown in for good measure—some new phenol derivatives created as possible sleep-producers but discarded as useless. When they arrived, Putnam was temporarily tied up with another research job and he called in an assistant.

"I'm up to my ears in work," said Putnam. "Can you run the tests on these?"

"Sure," said the assistant. "How many have you got? Seventy? Well, it'll take a little time, but I'll get started."

Each of these drugs was tested with a simple, ingenious machine devised by the Harvard workers to administer an exact electrical shock to a cat. They first found how much electricity it would take to put the cat into a fit. Then they gave the cat a dose of the drug, waited until it had been assimilated, and again measured the convulsive dose of electricity. Around the laboratory, it was known as the "cat-fits technique." It was a vital part of this job of drug-hunting; without it, the job might have taken years.

"If the drug doesn't let a cat stand a larger shot of electricity," the scientists explained, "then the drug is no good. But if the drug builds up the cat's resistance to electric convulsions, then maybe we have something."

In three weeks, they had something. "There are three compounds here," they announced, "which look pretty interesting. . . ."

One of them prevented convulsions but unfortunately produced virtually staggering "burps." This one was discarded.

The second also prevented convulsions, but it tasted frightful. It, too, was discarded.

The third was di-phenyl-hydantoinate. It just seemed to prevent convulsions.

"How does it compare with bromide or phenobarbital?" asked Lennox.

"About ten times better."

Di-phenyl-hydantoinate—soon to be known as *dilantin*—was next taken over by stubby, practical, hard-working Dr. Houston Merritt, who, with the Parke, Davis experts, put it through the most rigorous tests. It was given by stomach tube to cats, dogs, rats, mice, and guinea pigs. It was injected into their veins and their bellies. It was given in small doses, medium doses, and large doses. It was given once a day, twice a day, three times a day, ten times a day. It was given to some animals day after day for months on end, while the scientists watched for any sign of poisoning. This drug, they knew, might have to be taken daily for years and perhaps for life by epileptic patients; it had to be safe.

At the same time, the Harvard workers checked their results with the electroencephalograph, the new "brain-wave machine" which had been developed a few years before in Germany and improved under Lennox's teammates, Fred and Erna Gibbs. This brain machine showed electrically what the brain was doing; it revealed that an epileptic attack is accompanied by a veritable electrical brain storm, an outpouring of large electrical currents. It could tell when a brain was normal and when it was epileptic. It could help to diagnose the disease, indicate its severity, tell when it was getting better or worse, and measure the effect of any proposed treatment.

"And now it told us in electrical terms even more than what we had already seen with our eyes," Lennox declared. "It told us that dilantin was effective against disturbed brain rhythms as well as against convulsions of leg muscles. It was obviously, unquestionably effective—in animals."

In March, 1936, dilantin had been tested and found safe enough to be used on the first patient. He was a thirty-year-old Italian who, late one night, was carried into the emergency ward at Boston City Hospital.

"We found him on the street," reported the policeman who brought him in. "He was having fits something terrible!"

The patient was no stranger around the hospital, where he had been treated for years, a victim of apparently uncontrollable epileptic seizures. His convulsions came so often that he couldn't hold a job. Not even massive doses of bromide or phenobarbital would help him.

"When they brought him in this last time," one of the doctors recalled, "he had so much phenobarbital in him that it was running out of his ears. Didn't do him a damn bit of good."

Interns and nurses put the patient into bed and left him there under observation. From his past record, they felt he would probably have another attack before morning. And then one of the interns thought of Dr. Merritt.

"Maybe we ought to tell him that this guy is back in here again," he suggested. "He and Putnam have some new drug they're working on . . . "

Dr. Merritt, summoned by telephone, came to the hospital and looked at the patient. "How're you doing, Tony?" he asked.

"Not so good, doc. I had a bad one tonight. The cops, they hadda bring me in here. Jeez, I dunno how long I can keep this up. Can't you gimme some medicine to stop it?"

Merritt grinned. "Sure, I think we can give you something. How'd you like to try a new one we've fixed up here?"

"Sure. Sure, doc. Anything you say."

A few minutes later Tony took a glass of water in which had been dissolved a little white, slightly pungent powder. "What's gonna happen now?" he asked.

Merritt patted his shoulder reassuringly. "If we're lucky, Tony, nothing will happen—nothing at all."

Nothing did happen. The expected convulsion didn't come. And the next day, with a little more of the powder dissolved in water and given to the patient, there was still no seizure.

"Keep taking this stuff three times a day," Merritt ordered.

Dilantin, taken three times a day, stopped Tony's epilepsy—not for a day or a week or a month, but permanently. He could live once more like a human being. He could go back to his job—it happened to be in a Boston necktie factory—and thereafter Merritt was flooded with a steady stream of the biggest, brightest neckties in Massachusetts.

The news of this preliminary triumph was brought to Lennox. It was the answer to his prayers, the result of nearly twenty years of ceaseless work. "That sounds very good," he murmured. "But you should try it on more patients."

A few days later, he and Merritt were in a hospital room examining a young girl who had been brought from Illinois for help. She had been suffering more than half a dozen violent attacks a day. Even while the doctors were in the room, she suddenly went into a seizure.

"Here's one for you right now," said Lennox. "Can your dilantin help her?"

"Maybe," answered Merritt. "We'll give it a try."

Dilantin worked. That was the last epileptic seizure she ever suffered.

Another patient was a fifteen-year-old high-school boy who had been a victim of epilepsy for years, and who was now suffering major attacks every day. Neither bromide nor phenobarbital could help him, but dilantin stopped his attacks almost like magic. He was completely well for nearly a year, and then one night he went to a school dance, forgot to take his medicine, and the next day suffered two seizures. Back on his three-a-day treatment, however, he was freed from his attacks once again.

In June, 1937, the Harvard team reported their preliminary results. "Clinical trials are now in progress," they announced. "The early tests are encouraging."

A year later, they appeared at the annual convention of the American Medical Association in San Francisco and reported their results on one hundred and eighteen patients suffering from major

epilepsy. "In nearly 30 per cent," they said, "there was a marked reduction in the number and severity of attacks. In nearly 60 per cent, there was complete relief."

Furthermore, when this drug was properly administered, it produced no skin rash, no stupor, no grogginess.

Oddly, dilantin—discovered in the first batch of phenol derivatives sent to Harvard—was the best drug that the Harvard men could find. They eventually tested more than a thousand chemicals, but dilantin was the only good one.

These and similar reports given by Tracy Putnam and Houston Merritt brought forth thousands upon thousands of letters, telegrams, telephone calls, and cables from overseas. Physicians, parents, and the victims themselves sent their blessings to the two researchers. Dr. Lennox, at his own insistence, remained very much in the background, and emphatically claimed that this was none of his doing, that Putnam and Merritt did all the work, and that they deserved all the credit.

"By definition, epilepsy is a condition which cannot be helped," he declared. "Everybody told these two men that they shouldn't waste time on it. But look what they've done—they've given us the most effective anticonvulsion drug that we have ever known!"

V

Dilantin, later experience showed, could relieve about three-quarters of the symptoms of three-quarters of the patients suffering from epileptic convulsions, and in many of them it could prevent the seizures entirely. It was not, however, a "cure for epilepsy," and most patients had to take dilantin several times a day as long as they lived, although occasionally—as the ancients had known—the disease sometimes stopped all by itself.

"There is a natural tendency for epileptic patients to get better as they get older," Lennox declared.

Although it was no complete cure, dilantin allowed thousands of epileptics to live normal lives. It permitted most of them to look

forward to going to school, getting married, having children, holding nearly any kind of a job, and, in short, living like other people. Like diabetics with their insulin, epileptics merely had to be faithful in taking their dilantin.

There was, unfortunately, one type of epilepsy in which dilantin and all other drugs were close to useless. It was a relatively infrequent type accounting for about one-tenth of all cases of epilepsy, but it was particularly pathetic since most of its victims were children. Medical men called it *petit mal,* the "little sickness."

Unlike the major and most shocking form of epilepsy, *grand mal,* with its violent convulsions, tongue biting, and foaming at the mouth, *petit mal* is marked by short losses of consciousness which may occur from once to twenty-five or fifty times a day. Each of these temporary mental black-outs lasts only a few seconds, rarely more than half a minute. The attack may be accompanied by a momentary rhythmic twitching of the face muscles, sometimes the only sign that a parent may notice. In still other cases, the affected child may suddenly lose his postural control; without warning, he will fall down and then pick himself up.

To the early medicine men who ascribed epilepsy to the work of the demons, it must have seemed that the victims of *petit mal* were cursed by only a very little devil. It was a devil, nonetheless, for it made the child slightly different from his fellows—and a "different" child is an outcast.

To Bill Lennox, now grayer with the passing years, *petit mal* was another challenge which must be met. He was still the medical missionary, still wanting to be helpful—and there were perhaps a hundred thousand children in America alone who needed his aid.

"Cowboy Bill spent his life acting as if the entire field of epilepsy was his personal responsibility," one of his colleagues claimed. "He just didn't know how to stop."

So Lennox went to work again, back to the laboratories, urging more men to do more research; he went to the big drug companies, asking them to test every new compound on convulsions and seizures; he went to the big foundations and to patients and their

friends, asking for more and more money—not for himself but for research projects, for educating patients, for educating physicians, and for educating educators.

"It is exceedingly odd," he remarked, "that so many schools and colleges are loath to admit students with epilepsy, even though their attacks may be controlled by dilantin. Under present-day rules, it seems that no modern military academy would accept such eminent epileptics as Julius Caesar and Napoleon Bonaparte. And no modern theological school would enroll a student exhibiting the symptoms ascribed to Saint Paul!"

During his constant battle for the victims of all kinds of epilepsy, Lennox never forgot the tens of thousands of children suffering from *petit mal;* their problem was perhaps the closest to his heart Yet there was little he could do for them until a group of workers in Chicago happened to start on a series of fortunate incidences.

In 1940, at the Abbott Laboratories, chemist Marvin Spielman was asked to create some new kind of painkiller which might be marketed as a competitor to aspirin. He went to the library, read up on the recent discoveries here and abroad, and decided to look into a new group of compounds recently studied in Switzerland. These were the oxazolidine derivatives, synthetic compounds found only in a laboratory.

Dr. Spielman proceeded to create a whole mess of compounds; among them were a number of these oxazolidines, one with a methyl group added here, another with two ethyl groups hung on there, a third with both a methyl and an ethyl group, and so on. When he had a few dozen of them purified, he began shooting them over to Dr. Richard K. Richards, Abbott's intense, birdlike, Greek-and-Latin-quoting drug expert.

"I tested the first fifteen," Richards reported. "Nothing worth while. I threw them out."

The sixteenth was an ordinary white powder carrying the imposing name of 3,5,5-trimethyl-oxazolidine-2,4-dione, soon to be shortened to *tridione.* Tridione was definitely not thrown out.

"It prevents pain in relatively small doses," his report continued.

"Its toxicity is very low, it is nonirritating, and there are no apparent side-effects in animals."

In human beings, tridione seemed to be a highly useful drug. Richards tried it on his own patients and sent some of it for further trials to medical friends in New York and Baltimore. It appeared to be at least as good as aspirin, especially helpful after surgery and for the relief of gall-bladder attacks and stomach aches. In his own office, some of the stenographers and lady laboratory assistants tried it for menstrual pain, and some of them announced delightedly that it was one of the best things they had ever taken.

Only after a considerable number of human tests was it discovered that tridione was not an altogether reliable painkiller. Sometimes it worked, sometimes it didn't. And sometimes—in about half the adults but apparently never in children—it temporarily interfered with color perception in bright sunlight. Tridione was shelved, at least for the time being.

Meanwhile the chemists had been working on another series of chemicals—this time a series aimed at quieting jumpy, spasmodic intestinal, uterine, and urinary-tract muscles—and, as usual, sent their creations to Dr. Richards for testing on animals. From this new packet of proposed remedies, Richards selected one now called *amethone* and reported that it might be useful in controlling spasms of the muscles involved in kidney colic, intestinal spasms, and menstruation. The word "menstruation" struck a familiar chord.

"Didn't we have something else around here that we were using for menstrual pain?" he asked.

"Sure," said one of his coworkers. "It was that analgesic, tridione."

Then another spoke up. "Say! Why don't we try a combination of tridione and amethone? Amethone ought to keep the uterus muscles relaxed, and tridione ought to relieve the pain. . . ."

Here, it seemed, was a million-dollar idea—if it worked. But amethone was still an untested drug and nobody had any idea how it would work in combination with tridione. In the summer of 1943,

Richards put a technician on the job. "Try these two on mice," he said, "and see what they do in combination."

What they did in combination was, at first, a complete surprise. In large doses, amethone was known to produce convulsions; yet when even large doses of amethone were combined with a little tridione and injected into mice, the mice flatly refused to convulse.

"Wonderful!" said Richards. "Tridione must therefore be an anticonvulsant. Perhaps it may be useful in epilepsy."

Now Richards, with Dr. Guy Everett, began an intensive test of convulsions and the ability of tridione to prevent them. Instead of working only on electrically convulsed cats, as the earlier dilantin researchers had done, they produced convulsions in their animals by giving them injections of metrazol, strychnine, picrotoxin, cocaine, and other chemicals. In such animals, tridione proved itself to be an excellent cure or preventive for convulsions. Given beforehand to mice, it completely prevented the seizures; given even while the mice were in the midst of convulsive attacks, it stopped the seizures within two minutes.

Just as these animal tests were completed, Richards received a letter from a scientist at the University of Vermont. "Do you have any new drugs which we might investigate?" asked the Vermonter.

Richards wrote: "I am sending you a new compound which we think might be used in cases of epilepsy. It is called tridione. . . ."

Tridione was tested on animals at the university and then was sent to the state school at Brandon, Vermont, where Dr. Douglas Thorne tried it on half a dozen children suffering from *grand mal* epilepsy. These children were in a deplorable state; they were not only epileptic but also mentally wrecked. Yet, Thorne reported, tridione seemed to help them and to prevent some of their *grand mal* convulsions.

At Chicago, the report from Vermont was not received with any great jubilation. "Seemed to prevent" convulsions? Was that the best that tridione could do? Richards and his colleagues had expected something better than that!

Then into the picture came Dr. Meyer Perlstein, a husky,

enthusiastic pediatrician on the clinical staff of Chicago's Cook County Hospital. "Got any new drugs these days?" he asked Richards.

"We've got something for epilepsy," said Richards, "but I'm not at all sure what it will do."

"Bring some over," Perlstein boomed. "We'll try it."

A few months later, in January, 1945, the two men presented their laboratory and clinical findings before the Chicago Neurological Society. They had administered tridione, they said, on nearly forty children. About half were victims of *grand mal*, of the convulsion-type of epilepsy, and on them the new drug was of only slight value, perhaps about as useful as bromide. *But the other children were victims of petit mal*—they had momentary black-outs five, ten, or twenty times a day, their faces twitched, and sometimes they fell inexplicably to the floor—*and on them, tridione was magnificent!*

The Abbott Laboratories men now went into a huddle. "If tridione is as good as it looks," said Everett, "we'd better give it a real trial. We'd better have it tested by the man who owns epilepsy."

Off went a letter to Bill Lennox: "We have recently developed a new drug, tridione. Chemically, it is 3,5,5-tri-methyl-oxazolidine-2,4-dione. We think it may be useful for *petit mal*. Would you be interested in undertaking further tests? . . ."

Back came the answer: "Delighted."

In Boston, Lennox had been fighting his usual battle against the inertia of many doctors.

"Why don't you forget epilepsy?" one of them asked. "You've got dilantin now. It's pretty good. Suppose it doesn't work in every kind of epilepsy, suppose it isn't 100 per cent effective? Why don't you take it easy?"

And another claimed, "You're wasting your time bothering with *petit mal* anyhow. It isn't so horrible. And most kids with *petit mal* will get better by themselves sooner or later."

Lennox took a very dim view of such arguments. "There are perhaps one hundred thousand victims of *petit mal* in this country,"

he said. "And even though the healing forces of nature usually bring a spontaneous cure, this distant prospect is of no great comfort to parents who find the educational and social progress of their children blocked by attacks which recur many times every day."

To him, tridione was useless against *grand mal,* but it was the long-awaited answer to *petit mal,* to "black-out" epilepsy. In his Children's Hospital wards, he tried it on a girl who had been having more than forty seizures a day for more than six years; within two months tridione reduced the attacks to one a week, and within another four months the attacks had stopped completely. He tried it on an eleven-year-old boy who had been blacking out twenty or thirty times a day for six years; two months after tridione treatment began, his seizures disappeared and did not return even when the medicine was discontinued.

These children, soon followed by scores of others, quickly began to eat better, put on weight, win better marks in school, and—of particular importance—get along better with their parents, their teachers, and their playmates.

In these children, except for an occasional rash or sensitivity to light, the drug operated smoothly and safely. Only later would it be found that in a very small percentage of patients, tridione can damage the blood system and sometimes even cause death. But, for an overwhelming proportion of boys and girls, it was remarkably safe.

In July, 1946, the American Medical Association convened again in San Francisco, eight years since the AMA had met there before and since the day when Tracy Putnam and Houston Merritt had reported their first big series of *grand mal* patients treated with dilantin. Now Bill Lennox—he was sixty-two, grayer and more stooped than ever, still shy and retiring—came to give his report on tridione.

He presented his results on one hundred and fifty *petit mal* patients. "None of this group," he began, "experienced complete relief from previous treatment and few had had even partial or temporary benefit."

Now he had been given the opportunity of trying a new remedy, tridione.

"During the past months," he said, "I have given this drug to many patients, both children and adults. . . . There is nothing in the history of epilepsy which would prepare one for an abrupt decrease or wiping out of these seizures in a period of days or weeks. . . ."

Yet tridione, in his hands, had completely wiped out the attacks in nearly 30 per cent of his patients, and reduced them by more than three-quarters in another 50 per cent.

"In my experience," he concluded, "it has been most dramatic."

So, at last, "Cowboy Bill" Lennox, the man who wouldn't quit, was pushed into the spotlight and forced to take his bows. He, himself, had discovered no cures; the miracle-working dilantin and tridione had been found by others, and it would be other men who would find still better drugs which were sure to come. But to physicians and research men all over the world, it was Bill Lennox who had led the fight.

It was he who had triumphed over professional bewilderment and defeat, who had conquered despair and hopelessness.

It was he who had driven out the demons of epilepsy.

CHAPTER XIII

Atomic Medicine

BECQUEREL, THE CURIES, AND THE ATOM-SMASHERS

LATE on the night of January 5, 1896, young Ernst Lecher burst into the office of the *Wiener Presse*, Vienna's great newspaper.

"Is my father in?" he asked. "I must speak with him at once!"

"One moment, Herr Doctor," answered the receptionist. "He is in a most important conference and . . ."

Dr. Lecher interrupted. "Go and get him. Tell him—tell him I have something more important than any meeting!"

A few moments later, he was with his father, Z. K. Lecher, publisher of the *Presse*. "What is it, Ernst? What is it? Is anything wrong?"

"Wrong? No, but I have the most amazing, the most remarkable, the most colossal story for you—I have rushed all the way to tell you—you must listen to me. . . ."

"But I am listening, Ernst. Tell me, what is all this about?"

The young doctor paused long enough to take off his hat and coat, still covered with snow, and throw them on a sofa. Then he leaned over his father's desk.

"Tonight," he continued, "I was invited to Professor Exner's—you know him?—and he showed us some photographs sent from Würzburg. Photographs taken through solid wood, through flesh. I have brought some with me—here, just look at these!"

Publisher Lecher picked up one. "What is this?"

"A photograph of some metal weights inside a wooden box."

"Inside a box? Nonsense, one cannot see through a piece of wood!"

"But it is not nonsense, father!" the doctor insisted. "This has been done with a new kind of light that *can* penetrate wood."

"What's this other photograph, bones?"

"Yes. This is a photograph of the bones inside the hand of a living woman—here, these are the phalanges, and these are the metacarpals, and this big black thing here is a ring she is wearing."

"You mean . . ." The older man swallowed. "You mean to tell me that this new kind of light can also penetrate flesh?"

"Yes! Yes! Right through living flesh! It can show us what our eyes cannot see. Think, father, think what this will mean to medicine. It will let us look inside the living body, it will let us see where bones are broken, perhaps where bullets have lodged. Never has there been such a discovery!"

Lecher stared at his son. "Are you—I mean, this is no . . ."

"It is no fake, father," said Ernst. "These pictures were made by a distinguished scientist, a man of the highest reputation. Exner told us all about it. A scientific report will be published in a few days."

Lecher was a newspaperman. If these photographs were not a fraud—and there was no reason why his son would deceive him—then here was one of the great newspaper stories of his life! Here, by the gods, was a device to take pictures of the invisible!

"Ernst," he asked, "who is the scientist who discovered this thing?"

"He is professor of physics at the University of Würzburg. His name is Roentgen. Wilhelm Konrad Roentgen."

And so, the following morning, the *Wiener Presse* carried the first report of the discovery of Roentgen rays, soon to be known as X rays. Its impact on the public was tremendous. In the restaurants, the coffeehouses, the laboratories, and the hospitals, it was the topic of a thousand excited conversations. That night, news of the discovery was cabled to London and then all over the world.

"It is announced," read the cable dispatches, "that Professor Routgen"—the inevitable typographical error—"has discovered a light which for the purposes of photography will penetrate wood, cloth, and most other organic substances."

Never had a scientific discovery been given to the public with such speed. Before Professor Roentgen had a chance to announce it himself—which he did on January 23, 1896—it was published in hundreds of newspapers, magazines, and scientific periodicals. Since the details of construction of the X-ray tube had also been reported in some of these publications, other scientists in Germany, England, France, and America began to build their own, and doctors, engineers, photographers, physicists, and biologists predicted special applications for the new "all-penetrating rays."

The future use of X rays was, naturally, misunderstood by many. In the state legislature in New Jersey, an assemblyman introduced a bill to prohibit the use of X rays in opera glasses at theaters, and in London, one firm did a land-office business by advertising the sale of "X-ray proof underclothing" for women.

In Chicago, a young medical student, E. H. Grubbé, who ran his own commercial laboratory, was one of the first to build his own X-ray machine. He tried it only a few days after the *Wiener Presse* announcement, and discovered to his delight that he could photograph his own finger bones right through the flesh of his hand—and, apparently, without any pain, discomfort, or danger. Only after he demonstrated this feat many times a day did he begin to question the safety of the apparatus.

"Look at my fingers," he told a group of his teachers. "They're red, and itchy, and they're beginning to hurt!"

Most of the physicians were surprised—after all, no one had yet reported that these X rays might be at all dangerous!—but one of them, Dr. J. E. Gilman, had an idea.

"Looks like those mysterious rays of yours can burn living tissue," he said. "They can probably destroy diseased tissue, too. Does it hurt much?"

"Well, not really," answered Grubbé. "It's uncomfortable but not very painful."

"That *is* remarkable—rays that can burn tissue without causing pain."

And then Dr. Gilman presented his idea. "Say! Why not use those rays to burn off cancer tissue? It shouldn't hurt much, and it might just possibly work!"

On January 28, 1896—only twenty-three days after the world first heard of X rays—a Mrs. Rose Lee was referred to Grubbé's workroom on Pacific Avenue. She took her first treatment the following day, for a malignant tumor of the breast. The treatment came too late for her, since she died a month later, but X rays had entered the fight against cancer.

II

When Professor Roentgen's sensational new tube was in operation, its interior was lit with a pale, apple-green glow, much like that of phosphorescence. In the laboratories at the Polytechnic School in Paris, a famous bewhiskered professor considered that glow and felt that it held the secret to X rays.

"When the tube is not working," he said, "there is no phosphorescence and there is no Roentgen ray. But when the tube works —ah, then there is phosphorescence and then there is the ray. It is of a certainty—there is a connection between phosphorescence and Roentgen rays."

The professor—forty-four-year-old Henri Becquerel—was convinced that this was so (it happened to be wrong) and he proceeded forthwith to investigate it. Becquerel came by his mistake naturally. His father, Edmond Becquerel, had been one of the pioneers in the study of fluorescence and phosphorescence. Discussions of these phenomena had been as familiar a fixture as coffee and rolls at the Becquerel family breakfast table, and Henri had grown up in an atmosphere of the phosphorescence of zinc sulphides, of phosphorus, and of uranium.

"If the phosphorescence in M. Roentgen's tube produces the rays," he said, "then it seems that the phosphorescence in some of these chemicals—say, in sulphides or in uranium—should do the same thing."

Which should he use at the start, sulphides or uranium? Becquerel happened to have some uranium salts in the laboratory. He started with uranium. It was, as he himself remarked later, "a decision of the most happy coincidence."

To produce this strange phenomenon of phosphorescence, as Papa Becquerel had shown years before, you take a proper chemical and expose it to strong sunlight. Then you take the chemical indoors, into a dark room, whereupon it appears to shine with a ghastly, luminous, apple-green glow.

Henri Becquerel performed exactly such a manipulation with his crystals of uranium salts, modifying it, however, in order to detect any X rays which might be present. X rays, unfortunately, are ordinarily invisible to the human eye. They can be detected—as Roentgen had shown—on a photographic film wrapped tightly in black paper. Visible light can't penetrate that paper, but X rays can. So Becquerel, in February of 1896, took his crystals of uranium salts, set them on top of a photographic film which had been wrapped in black paper, and placed them outside in the winter sunlight. Hours later, he removed the film, developed it, and announced, "It is as I had surmised. Where there is phosphorescence, there are the Roentgen rays!" For when the film had been developed, it showed the shadowy picture of the uranium-salt crystals which had been sitting above it.

"One must conclude from these tests," he declared, "that the phosphorescent substance emits radiations which penetrate black paper that is opaque to ordinary light."

The hypothesis, thus, could be accepted as proved: phosphorescence produces X rays. Becquerel believed this, but he was just as wrong as he could be. He discovered his error himself; he discovered it because he was a scientist, and the son of a scientist, and even the grandson of a scientist, and he always repeated his

experiments. Day after day he went through the same manipulations, and day after day he got the same results. Uranium, put in the sunlight, became phosphorescent. Phosphorescent uranium, when lying on top of a photographic film, could expose that film —and expose it right through several sheets of lightproof black paper.

On February 26, 1896, however, clouds covered the sky over Paris, and the sun came through only intermittently. "We will not make the experiment today," decided Becquerel, and he left the complete setup in a dark drawer—the dull, drab, unphosphorescent crystals of uranium, sitting on top of the photographic film wrapped in two thicknesses of black paper. On the twenty-seventh, twenty-eighth, and twenty-ninth the weather in Paris remained cloudy, and the uranium and the film remained in the drawer, brewing one of the great miracles of modern science. On March 1 Becquerel opened the drawer, took out the film, and handed it to his assistant.

"There will be nothing on here—perhaps the faintest of images," he said. "But develop it anyhow. . . ."

It was developed. It showed the outlines of the uranium crystals. The picture was not dim or weak but actually more intense than any which Becquerel had ever seen.

"Name of a name!" he fumed. "It is impossible! The uranium sat like a lump of coal in the dark. It had no sunlight. It was not phosphorescent. And yet, of a certainty, it has emitted rays!"

He thumped on the desk and called again for the assistant.

"Did you tamper with this?" he demanded.

"Monsieur!" replied the aggrieved assistant.

The next night, Professor Becquerel attended the regular meeting of the Academy of Sciences and announced this most vexing discovery—vexing because, as he said, "It is not of the phenomena which one could have expected to observe."

Still assuming that the invisible rays must be related in some fashion to phosphorescence, he proposed that they represented a long-continuing aftereffect of phosphorescence. "It may be like

a kettle which continues to give off heat for a long while after it has been removed from the flame," he reasoned. How long, then, could unphosphorescent uranium—uranium not exposed to sunlight—continue to give off the invisible radiation? He started a new batch of crystals on March 3 and tested them forty-eight hours later; the rays were still coming. He tested them on March 9, and still they were there.

"Peculiar!" he said.

He tested them on March 18—and still no letup.

"Their persistence," he declared, "is prodigious!"

And even in November, the uranium was still producing rays, and producing them with remarkable constancy. With the best measuring devices which Becquerel had at hand, he could find not the least drop in intensity! Furthermore, he found that these rays could penetrate not only black paper but also cardboard, copper, aluminum, and platinum. They could go through water. They continued to appear even though the uranium salts were dissolved in water—a process which generally quenches phosphorescence. They affected air so it would carry an electric current. And, of even more importance, the rays were produced not only by the particular uranium salts which Becquerel had used at the beginning but also by every other uranium compound which he could borrow from his friends.

"I propose to call them 'uranium rays,'" he told the Academy. "There are important differences between them and those of M. Roentgen."

One obvious difference was the source. Roentgen's rays came from a special kind of vacuum tube powered by electricity. "What, then, is the power which uranium contains?" asked Becquerel. "From where does its energy come?"

By November, 1896—scarcely ten months since Roentgen's discovery of X rays had been reported and had started this uranium research—Becquerel realized that the amazing radiation from uranium had nothing to do with phosphorescence. This was something else.

III

A year later, two other scientists almost simultaneously picked up Becquerel's work and attempted to carry it further. One was Gerhard Karl Schmidt, a British-born German physicist, then conducting research at the University of Erlangen. The other was Marie Curie.

At the age of thirty, Marie Sklodowska Curie was an almost fanatically zealous Polish woman who had come to Paris, won two university degrees while living for months at a time on a semi-starvation diet, written a monograph on the magnetization of tempered steel, married Pierre Curie—a professor of physics at the Municipal School—and given birth to her first child, Irène. When she had recovered from childbirth, Marie decided to continue toward her doctor's degree. She and Pierre sat up night after night, discussing various possible subjects for a thesis, and after weeks of indecision, they selected a likely topic—a further investigation of Professor Becquerel's "uranium rays."

"But where can I do the investigations?" asked Marie. "Where can I find a laboratory?"

Pierre found her a "laboratory"—a dirty, cold, drafty, wet little storeroom on the Rue Lhomond. The equipment was poor, the laboratory facilities were miserable—or nonexistent; the only useful device was a new type of electroscope devised by Pierre and his brother, Jacques, a device which could *measure* the potency of the uranium rays. But this abominable excuse for a laboratory was fated to be the scene of one of the most inspiring stories in the annals of science. Part of that story, telling of great achievements made in the face of nearly unbelievable obstacles, has been related many times. In its scientific elements, it is simple and surprisingly brief.

At the start, early in 1898, Marie knew only what Becquerel had reported to the Academy, and later described to her in person: A number of uranium compounds produce, apparently spontaneously, an invisible radiation which can penetrate many opaque

substances; that radiation can be detected photographically; it also can be detected with an electroscope.

"Is uranium the only chemical substance which produces these rays?" she asked.

"I do not know," answered Becquerel. "It is the only one among those which I examined. But I did not examine all the elements."

Marie, therefore, began by testing every known chemical element. In a few weeks, she had her answer—this strange activity, which she soon called *radioactivity*, was possessed not only by uranium compounds but also by thorium compounds. Even as she considered the meaning of this fact, Gerhard Schmidt in Erlangen announced the same discovery; he, too, was now hot on the trail of the mystery.

And then Marie made the surprising finding which Becquerel had missed. "The more pure the uranium," she revealed, "the less is its activity!"

Here, then, was convincing proof that radioactivity is not a monopoly of uranium. Actually, she found the most intense radioactivity coming from a crude ore which contained only one part of uranium to one part of impurities. It was an ore called pitchblende, sent from the mines at St. Joachimstal in Bohemia.

On April 12, 1898, she announced the "probable presence" in pitchblende ores of a "something" endowed with powerful radioactivity.

The Curies—Pierre had dropped his own work and joined forces with Marie—now managed to get two hundred pounds of pitchblende ore. When it arrived at their miserable little shed, they cooked the stuff, boiled it, filtered it, and crystallized it. After each step, they used their invaluable electroscope to see where the "something" had gone, whether it was in the crystals or in the liquid, in the concentrate or—heaven forbid!—in the discard. After three months of work, Marie and Pierre together reported to the Academy of Sciences the detection of a chemical element new to science.

"We propose to call it *polonium*," they said, naming it after Marie's beloved Poland.

But was polonium the final answer? "No," said Marie, "there is still something else in there."

"There" was what remained of the shipment of pitchblende, now concentrated to a few pounds. The two Curies went back to work, and on December 26, 1898, they reported again to the Academy.

"During the course of our researches," they said, "we have encountered a second substance, strongly radioactive and entirely different from the first (polonium) in its chemical properties.

"We believe that this new radioactive substance contains a new element to which we propose to give the name of *radium*. . . . The radioactivity of radium must be enormous."

The Curies had found radium. They did not have it yet in pure form, only as a moderately concentrated, impure mixture, and it would take them four grueling years before they could actually look upon the pure element. But even this impure form had "enormous radioactivity"—enough to win it a place in medicine.

IV

Announcement of the Curies' discovery of radium came as a totally unexpected revelation to scientific workers all over the world. Some authorities hailed it as even more sensational than the discovery of X rays. In the United States—where the Spanish-American War had just ended—and in England, France, Switzerland, Austria, Holland, and Germany, physicists and chemists rushed to investigate for themselves the surprising new chemical lurking in crude pitchblende ore. Within a few months, they reported that the rays from radium could be divided into three entirely different types—the so-called *alpha* rays, consisting of high-speed particles of helium gas; the *beta* rays, electrons or units of electricity; and the *gamma* rays, practically the same as the X rays from Roentgen's X-ray tube.

From where did these different rays come?

From the slow, constant disintegration of radium atoms, from the transformation of matter into energy!

"But this is impossible!" proclaimed some older workers. "Such a change is ruled out by all our laws of matter and energy!"

"It is not at all impossible," replied their younger colleagues. "It is an observable fact. The laws of matter and energy must be changed. . . ."

At the same time, seeking to get extracts of radium for their own study, other scientists attempted to improve on Marie Curie's long and arduous method of isolation. One of these men was Fritz Giesel, a middle-aged German chemist in the quinine factory at Braunschweig.

"The method of the Curies," he said, "is too complicated. I can do it better."

By the summer of 1900, he not only had his remarkably improved process but was using it to furnish supplies to his scientific colleagues all over Germany. One day the local dentist, Friedrich Walkhoff, came to him and asked, "What effect does this radium of yours have on the skin?"

"I am sure I don't know," he answered.

"It would be interesting to investigate that," said the dentist. "Could you lend me a little sample?"

That same day, Walkhoff strapped to the skin of his arm a little paper sack containing a tiny amount of radium. He kept it in place for several hours, then removed it and examined his arm.

"Nothing has happened," he remarked. "On the skin, this radium has no effect."

Two weeks later, however, Walkhoff changed his mind. On the very spot where he had placed the radium, there was now an angry red mark which felt uncomfortably sore.

"How peculiar!" he said, and proceeded to write a short report which was eventually published in—of all places!—a photography magazine.

Later chemist Giesel tried the same experiment, keeping the

radium on the inner surface of his own arm for exactly two hours. He, too, noted the lack of any reaction for two weeks, then the appearance of the red, burning inflammation, and still later the slow healing process. He also tried radium on the leaves of green plants and observed that they soon became yellow and shriveled. He published his report in a German chemical journal.

Both Walkhoff and Giesel had become victims of radium burns, the results of overexposure to the powerful rays emanating from radium. They faithfully reported their findings, and they suggested that radium might well be handled with caution, but they carried the idea no further. In Paris, however, the Curies—especially Pierre, whose father and grandfather had both been physicians—were working on radium harder than ever, trying to get the element in pure form. With them was Professor Becquerel, the man who had started them on their way to discover radium and now was their warmest supporter; he claimed no credit for himself but toured Europe to talk about radium and "*les plus belles recherches*" of the Curies.

On April 3, 1901, Becquerel went to the Curies' laboratory to borrow a sample of the chemical. "It is for the purpose of making a demonstration," he said. "I am to give another lecture."

Pierre handed him a tube of radium—a little glass tube standing scarcely half an inch high, which was wrapped in paper and then in turn placed in a cardboard box. Becquerel tucked this securely into a corner of his waistcoat pocket.

"Have a care, Monsieur!" warned one of the men in the laboratory. "The stuff in that tube, it can burn you. I have just read that some men in Germany . . ."

"Nonsense," said Becquerel, and he went off to his lecture.

Two days later he returned to the laboratory and handed back the little tube of radium. Later he calculated that, during the two days, he had kept the radium near him for about six hours.

At first, as in the case of the two Germans, there were no effects. Then, ten days after his imprudent exposure, Becquerel awoke one morning to find that a red spot, hardly as big as his thumbnail,

had appeared on the skin of his belly. During the day, the spot became increasingly uncomfortable.

"It feels like a burn," he thought, "and it looks like a burn. But I have not burned myself." And then he realized that the "burn" was located right under his waistcoat pocket. "A thousand damnations! It was that tube from the Curies!"

He rushed to the Curie laboratory and announced the catastrophe. "I love this radium," he said, "but I've got a grudge against it!"

Pierre Curie solemnly reproduced the effect on himself by strapping a sample of radium to his arm for ten hours. Two weeks later, his skin broke out with the slightly painful redness, and later with blisters and a scab. Marie, now that it was called to her attention, realized that she, too, had been suffering from similar but less severe skin reactions; her fingers, which had held containers of radium for several minutes every day, were dry and peeling, and her fingertips were hard and painful.

The Curies, totally immersed in their researches, could not make themselves seek medical attention, but Becquerel decided that a doctor should dress his wound.

"I shall get the best man in Paris," he declared. "I shall go to old Besnier."

Dr. Ernest Besnier—he was then seventy years old—was a close friend of the Becquerel family. He was, moreover, head of the dermatology department at St. Louis Hospital and one of the greatest skin specialists in France, internationally famous for his studies on leprosy and on tuberculosis of the skin.

"My dear friend!" he greeted Becquerel. "You are the veritable picture of health. Your color, it is admirable. What can bring you to my office?"

"I have a red spot."

"Ah? A red spot? Where is it?"

"It is on my abdomen," said Becquerel.

"How interesting," remarked Besnier. "May I examine it?"

Becquerel exposed his wound, and the old doctor regarded it

carefully. "Did you, by chance, acquire this burn from one of M. Roentgen's X-ray machines?"

"No," said Becquerel. "I got it from radium. But why do you ask about Roentgen?"

"Well, recently I have seen a number of these spots which have resulted from overexposure to X rays," replied Besnier. "Yours, it has the exact same appearances. Ah, this radium of yours—how does it work?"

Briefly, Becquerel sketched the nature of the newly discovered chemical, its isolation by the Curies, and its production of rays—rays which could go through black paper, pasteboard, aluminum, copper, and glass, and which evidently could burn human skin.

"That one is a very interesting chemical," commented Besnier. "I think it might have some use in medicine. Maybe it could do what X rays can do. Maybe it could destroy diseased tissue. Maybe it—but there is no use in talking about such possibilities. There should be investigations."

"Would you like to perform such a study?"

Besnier smiled. "At my age, one does not commence this kind of undertaking. But there is a brilliant man who is working with me now. He might be just the one to do it. Could you get him some of this wonderful chemical?"

"I shall speak to Professor Curie about it in the morning," said Becquerel.

The man who was recommended by Besnier to make the first trials of radium on a human patient, and who soon was entrusted with some samples of radium by Pierre Curie, was Henri Danlos of the St. Louis Hospital. He was, all things considered, an unfortunate choice. Dr. Danlos was known throughout Europe for his researches in dermatology. He had investigated and developed new treatments for tuberculosis of the skin, psoriasis, acne, and skin cancer. He had also originated the use of organic arsenic compounds for the treatment of syphilis. He was famed as an energetic, ingenious, imaginative investigator, just the sort of a man who might be selected to try a new medical agent. But Danlos

was now sick and very unhappy, restless and pessimistic and often in great pain.

"I will be honored to try your radium," he told Pierre Curie, but his efforts turned out to be only halfhearted.

He tried it first on four patients suffering from an obstinate, unpleasant but quite rare chronic affliction known as lupus erythematosus, a condition marked by eruptions of flattish red pimples. Radium treatment—little containers of radium applied for many hours at a time to the afflicted areas—seemed to help, first producing a mild, reddish, relatively painless "radium reaction," and later replacing this with good, healthy tissue. Then he used the same treatment on a more common disease, tuberculosis of the skin, and on the itchy, unsightly patches of psoriasis, and on evil-looking "port wine" birthmarks. He even used it on cancers of the skin.

In all these diseases, he satisfied himself that radium had value "within certain restricted limitations," but he soon decided that these limitations were too severe and he went back to treating his patients with more ordinary drugs and with X rays.

Other physicians in France, England, and Germany quickly repeated his preliminary studies and attempted to extend them, trying radium on all kinds of skin tumors, unsightly scars, birthmarks, eczema, warts, and a great variety of skin infections. Their studies were more careful, and their results were better than those of Danlos; nevertheless they, too, failed to achieve any startling advances.

"Except in the case of very benign lesions," one expert summarized, "we are able to report very few successes. We must draw the conclusion that, although radium has a very beneficial action, it cannot lay claim to the treatment of anything beyond small and innocent superficial sores—and these respond quite as readily to other types of treatment."

On the other hand, there were a few medical men who blithely proclaimed that a host of diseases would henceforward be cured

either by radium itself or by the use of water or air exposed to radium.

"Radium-air," declared one American doctor, "may prove to be very efficacious in the treatment of lung diseases, and radium-water in the treatment of stomach troubles. . . . Radiofied water has been used with marvelous effect in the treatment of diphtheria in its first stages. . . . During the prevalence of infectious diseases, water may be radiofied, instead of being boiled, to purify it for drinking." This same doctor warned, however, that "the advertising charlatans will doubtless reap a rich harvest from this new discovery, and I would enjoin the regular profession not to surrender it in their hands, but guard it with caution and use it with discretion."

He was right on one point. Charlatans quickly took over such wondrous-sounding agents as "radiofied water" and fleeced a gullible public out of millions of dollars. For a time, radium and radium products were widely advertised as sure cures for anemia, diabetes, high blood pressure, low blood pressure, gout, asthma, tuberculosis, indigestion, syphilis, sterility, pregnancy, and the common cold.

Nonmedical men likewise made somewhat uncautious predictions. "The heat rays of radium," calculated a French scientist, "are capable of melting stones, and of disintegrating, with great celerity, iron and steel, so that the effects of the exceeding heat of its rays will destroy fortifications, crumble battleships, and will extinguish human life like dew before the morning sun, thus rendering warfare impossible."

In 1903, the year that the Nobel prize was awarded to the Curies and Becquerel, Dr. Robert Abbe, surgeon to St. Luke's Hospital in New York, wrote to Marie and received from her enough radium to make one of the first and certainly one of the most careful radium studies in America. With this radium, he treated warts and skin tuberculosis and goiter, and he treated cancer of the skin, the ear, the breast, the lips, the mouth, and the tongue. He also intro-

duced a remarkable improvement which may well have come as a suggestion from Alexander Graham Bell, inventor of the telephone.

"I understand that the Roentgen X rays, and the rays emitted by radium, have been found to have a marked curative effect upon external cancers, but that the effects upon deep-seated cancers have not thus far proved satisfactory," Bell wrote. "It has occurred to me that one reason for the unsatisfactory nature of these latter experiments arises from the fact that the rays have been applied externally, thus having to pass through healthy tissues of various depths in order to reach the cancerous matter. The tube from which the Roentgen rays are emitted is, of course, too bulky to be admitted into the middle of a mass of cancer, but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material. Would it not be worth while making experiments along this line?"

Abbe prepared and used such small sealed containers to keep radium buried in the very center of a tumor for the proper number of hours or days, melting down goiters and breast cancers, and minimizing the destruction of near-by healthy tissue. In 1905 he introduced probably the most remarkable application of radium—radium treatment of cancer of the womb. This was a common and a terrible disease, causing perhaps one-half of all cancer deaths in women, difficult then to treat by surgery or X rays alone. Abbe used little sealed pellets of radium, small enough to be inserted into the womb and laid right next to the malignant tumor. In case after case, this simple and relatively painless method brought relief to afflicted women, destroying the tumor.

While this inspired doctor was leading American research on radium treatments, an even more significant study began in Paris under the direction of brilliant Dr. Louis Wickham and his energetic, bouncing Corsican colleague, Dr. Henri Dominici. These two, with their colleagues, worked in a special radium institute which Wickham organized, and made it possible for the first time

to put radium treatment on a scientific basis. They developed accurate physical methods of dosage, carefully measuring the strength of the radiation pouring out of each sample of radium and then correlating the size of the dose with the biological effect on tissues. They devised methods of "screening" the rays, using sheets of lead or aluminum to block those radium rays which served no useful purpose but merely irritated the skin. They instituted "ultrapenetrating" radium ray treatments. They used crossfire applications to hit deep-seated tumors. And above all, they repeated their studies on one patient after another, carefully comparing and analyzing and criticizing their results.

From 1905, when Wickham successfully treated his first patient —"an American lady from Chicago," suffering from cancer of the skin—until 1910, this group of workers used radium on some nine hundred patients, the largest number treated in a single institution. When they reported their findings, one fact stood unassailable—*used properly, used early enough, and used preferably in conjunction with surgery or X rays, radium can cure cancer!*

Now, for the first time, medical men appreciated the miracle which had been created by Becquerel and the Curies. Now, for the first time, they had a chemical—a fantastic, energy-producing, well-nigh unbelievable chemical—to use against cancer, most most terrible of all diseases.

V

At first, there was nothing so wonderful as radium. To physicists and chemists, it was a completely unexpected chemical element which spontaneously yielded energy, acting so slowly that its half life—the time required for one-half of any amount of it to disappear—was about sixteen hundred years. To physicians, and to many of their patients, it was a "cure for cancer"—only one of three such cures, to be sure, since surgery and X rays were also available —and the answer to prayers wrung from hundreds of thousands of dying victims.

"We will pay any amount of money for a cancer cure," these victims had said.

Radium was priced accordingly by the manufacturers. In 1910, the year that Marie Curie was awarded a second Nobel prize, pure radium could be bought at a price equivalent to about seven million dollars an ounce—but there wasn't an ounce of pure radium in existence.

Almost as soon as the Curies reported the presence of radium in Austrian uranium-bearing ore, the Austrian government announced that no longer would this ore be allowed to leave the country. Accordingly, geologists and mineralogists began looking elsewhere for other deposits of uranium, hoping that these deposits might also contain at least traces of radium. One of the first discoveries was reported in Colorado and Utah, where two Frenchmen found immense deposits of a uranium ore which they called carnotite. This lay untapped until 1912, when Joe Flannery, an ex-undertaker from Pittsburgh, decided to exploit it.

Flannery had long since left the undertaking business and made a small fortune, first by promoting a special bolt used in locomotives, and then by developing vanadium steel and organizing the American Vanadium Company. One day he learned that his sister was dying from cancer. "If we could have had enough radium in this country," her doctor told him, "we might have been able to save her."

Joe Flannery then and there embarked on a crusade to get radium—preferably from American ores—for American patients. He looked into the radium story, heard about the vast deposits in the Rockies, and went to work, incidentally giving up all his other interests. After spending fourteen months and fabulous amounts of money, he and his men succeeded in producing the first American radium. It was less costly than the European product but still fairly expensive—about $120 a milligram, or $3,600,000 an ounce.

Even while Flannery was getting started—it took him ten years to produce a little less than three ounces—a still richer source of radium was found in the Belgian Congo. This was discovered but

not announced immediately; World War I had already started, and the Belgian discoverers—fearing that a German victory was inevitable—decided to withhold their news. After 1918, however, the Belgians went to work on their radium mines and eventually were induced to cut the price to about $70 a milligram, or $2,100,000 an ounce.

Then, in 1930, two prospecting brothers, Gilbert and Charles Labine, came out of the Arctic circle with news that put a bright new name on the maps—Great Bear Lake, with a veritable treasure trove of uranium and the world's richest deposit of radium. In a few years, the price of radium came down to $25 a milligram, or $750,000 an ounce.

By the middle 1930's, the radium story seemed to be complete. It was still expensive, but most hospitals and many physicians could afford to purchase a supply big enough for their patients, and its medical applications appeared to be well understood. Yet, although radium was credited with helping to save thousands and thousands of lives, it was inherently unsatisfactory. There were many cases in which doctors wanted to give it internally, either by teaspoon or hypodermic needle, but this would have been both expensive and dangerous; once let loose in the body, radium goes to the bones and is deposited there permanently, continuing to send out its cell-killing rays until these rays may eventually kill the patient.

"What we need," claimed one expert, "is some substitute for radium, some radioactive chemical that gives up its energy not in centuries but in days or hours or even minutes. Such a substitute, if we could get it in large amounts, would be worth millions of dollars!"

The price that would eventually be paid was somewhat more than two billions. . . .

In 1911, a thin, friendly Hungarian aristocrat by the name of Georg von Hevesy came to the University of Manchester in order to study under Ernest Rutherford, the father of atom-smashing. Rutherford, credited with the ability to "arouse enthusiasm in

anything short of a cow or a cabinet minister," gave the young man what seemed to be a relatively simple research project.

"If you are worth your salt as a scientist," said Rutherford, "find some way to separate ordinary lead from the radioactive lead which is formed by the spontaneous disintegration of radium."

Von Hevesy failed. "In the following years," he reported later, "I tried numerous methods of separation without having the slightest success. It was a disheartening result."

Although one form of lead gave off energy and the other did not, they were otherwise almost indistinguishable; they acted the same way in acids and alkalis, in oxidizing agents and reducing agents, in the hottest flame and the coldest ice. Then, just before World War I, von Hevesy realized that this damnable twinlike resemblance of the two types of lead might be a blessing in disguise. From another source, he obtained a tiny amount of radioactive lead and deliberately mixed it with some ordinary lead. He couldn't separate them now, but he didn't want to—what he had was some "tagged" lead, a mixture of lead which could be virtually "seen" wherever it went.

Did the lead atoms, in a test tube, dissolve in acid and hook themselves to some chloride or nitrate or anything else? Von Hevesy, using delicate equipment to detect the rays coming from the radioactive lead atoms, could follow the process.

Did the lead atoms, in a different reaction, leave one chemical group and hitch on to another? Von Hevesy could pick up the "tagged" lead atoms and watch the migration.

Did the lead atoms go here or there, or land halfway in between? Von Hevesy could tell—not by means of long, arduous chemical tests but almost instantaneously with his ray-detecting devices.

It was just like putting a bell around the neck of one sheep in a flock and then using the sound of the bell to locate the entire group. "What we had," he said, "was *a method to trace atoms wherever they might go.*"

After the war, when he had moved to the Institute of Experimental Physics in Copenhagen, the Hungarian scientist joined

forces with biologists to trace radioactive lead and radioactive bismuth (also produced naturally by the disintegration of radium) as these atoms went up and down the stems and in and out of the leaves of bean plants, and in and out of the tissues of healthy and sick rats and mice and guinea pigs. For a time, this was as far as he could go. There was a great need to perform similar experiments with chemical elements more closely related to living tissues—elements like sodium, phosphorus, iron, calcium, and iodine—but radioactive, tagged forms of these substances were unknown. "They are not formed naturally from radium," von Hevesy explained, "and we cannot make them in the laboratory."

Some new atoms had already been formed in the laboratory. In 1918, Ernest Rutherford had finally achieved the goal of transmutation which had eluded generations upon generations of alchemists. Using the rays emitted by radium, he had transmuted nitrogen into oxygen. But his product, his laboratory-created oxygen, was exactly like the ordinary oxygen in the air—it was not radioactive.

In January of 1934, however, two physicists reported before the French Academy of Sciences that they had bombarded certain elements with the alpha rays coming from radium or polonium. They had bombarded boron and turned it into nitrogen. They had bombarded magnesium and turned it into silicon. They had bombarded aluminun and turned it into phosphorus. Furthermore, they announced, these final products—the nitrogen, the silicon, and the phosphorus—were radioactive. They spontaneously broke down to form still other substances and at the same time put forth rays of energy.

For the first time, man had succeeded in creating in the laboratory not merely one but three different potential substitutes for radium!

The discovery had been made in the great Radium Institute of Marie Curie, who now was dying from pernicious anemia and from years of overexposure to the lethal rays of radium. It had been made by thirty-three-year-old Jean Frederic Joliot, a thin,

handsome, sparkling, imaginative assistant to Marie, and his thirty-six-year-old wife, slim, grave, bushy-haired Irène Curie, the first-born daughter of Marie and Pierre.

The triumph of artificial radioactivity, soon to bring the third Nobel prize to be awarded to the Curie family and eventually to be a step on the road to the atomic bomb, was quickly confirmed in half a dozen laboratories. Other workers followed the Joliot-Curies and made radioactive forms of sodium, chlorine, iron, carbon, calcium, iodine, and half a hundred other elements. Now there were plenty of chemicals for von Hevesy's revealing "tracer experiments" on plants and animals and even man himself.

At first, however, only a few of these new radioactive elements were available, and then only in the tiniest amounts. The alpha rays from radium or polonium were not very practical for atom-smashing. Accordingly, in England and Germany and America, scientists and engineers went to their slide rules, their work-benches, and their drafting tables to design something better.

"We must provide a more intensive bombardment to smash an atom," they said. "We must find a superpowerful ray."

So they put together strange contraptions of condensers and transformers and vacuum tubes. They made electric devices which succeeded only in wrecking radio reception in homes all around their laboratories. They set up peculiar gadgets on the tops of mountains to capture the energy in bolts of lightning. They built enormous static-electricity machines and capped them with gleaming, polished metal spheres which proved to be irresistibly tempting to pigeons. One group tried to construct a great atom-smashing cannon—a straight tube through which the atomic bullets would be fired and, at the appropriate points along the tube, given added speed by properly timed electric "kicks."

At the University of California, young Ernest Orlando Lawrence considered this last idea, decided to improve it by firing the bullets through a series of such straight tubes, found this didn't work very well, and then figured out how to fix it.

"Instead of speeding up the particles by shooting them in a straight line," he said, "let's speed them up in a spiral."

He and his colleagues built a hollow tank to hold the particles and then placed around it the biggest electromagnets they could find. By reversing the charge on those magnets many times a second, they could make the atomic particles—nuclei of hydrogen or helium—whirl faster and faster in ever widening circles. Every time the particles went halfway around the circle, they were whipped to higher and higher speeds by an electric "kick." When these racing bullets were finally turned loose, traveling at tens of thousands of miles per second, they struck their targets—the atoms to be smashed or chipped or transmuted—with energies calculated in millions of electron-volts.

This new machine, first built in 1930, when Lawrence was twenty-nine, was the cyclotron. By 1934 he realized that where its predecessors could turn out radioactive forms of sodium, phosphorus, and other elements in barely perceptible amounts, the cyclotron produced them in relatively enormous quantities, equivalent to millions of dollars worth of radium.

To Ernest Lawrence, the cyclotron was not a device to help cure sick men and women. He was a physicist, interested not in medicine or biology but in the nature of matter and energy. He wanted the cyclotron to reveal the inner secrets of the atom. But this brilliant scientist had a younger brother John, and John was a physician.

In the summer of 1935, Dr. John Lawrence left his post on the faculty of the Yale Medical School and returned to California for a combined vacation and convalescence from a broken ankle.

"What are you going to do out here this summer?" asked Ernest.

"Not much. Hobble around until this leg of mine gets better."

"Um-m," remarked Ernest. "How about giving us some help?"

John shook his head. "Not me. I don't know anything about your cyclotron. I'm a physician."

"A physician is just what we want. The cyclotron is putting out

all kinds of rays—alpha particles and neutron rays and God knows what else. And we're making a lot of radioactive chemicals. Maybe they're safe and maybe they're not. We don't know what they'll do to us around the laboratory. We don't know even how to test them."

"That's simple," said John. "You just try them on rats or mice or . . ."

"Why don't *you* try them?"

So John Lawrence started to try the new rays and the new radioactive chemicals on experimental animals. In the first test, he put a rat in a small chamber and then put the whole thing into the beam of rays coming out of the cyclotron. An hour later he looked at the rat.

"Wow!" he exclaimed. "It's dead! Say, those rays are powerful. . . ."

Later, an autopsy report revealed that the rat had not perished from the effects of the cyclotron rays. Instead, the special chamber had been poorly ventilated.

"The cause of death," Lawrence decided, "was merely suffocation."

Soon, however, there was real evidence that the rays could destroy and kill; there was ample proof that the cyclotron scientists needed plenty of protection. For the next two years, he commuted back and forth between Yale and California, bringing his experimental animals from his Yale laboratory, exposing them to the cyclotron beam, and trying to continue his teaching. Finally, when he was offered an opportunity to join the University of California faculty, he decided to leave Yale and spend his full time on this new research.

"The possibilities were tremendous," he said. "I just had to spend full time on them."

These possibilities concerned primarily the new radioactive chemicals produced by his brother's cyclotron, substances which could do all manner of strange things. Radioactive phosphorus, for example, would be deposited in bones and teeth, steadily spray-

ing these areas with cell-killing rays for days at a time (not years, as was the case with radium); radioactive sodium would be spread all over the body, giving every tissue a gentle bath of these rays for many hours; and radioactive iodine would go straight to the thyroid gland up in the neck and release practically all of its rays in a few minutes.

Other scientists at the university came to watch early demonstrations, and many of them moved in permanently. This, they agreed, was intriguing stuff. One day, one of them brought up the subject of leukemia, an incurable disease in which the body is flooded and finally engulfed in a malignant overproduction of white blood cells. In normal men and women, the white blood count generally remains less than twelve thousand; in victims of leukemia, it may soar to a hundred thousand, a hundred and fifty thousand, or even more. In the United States alone, leukemia killed more than six thousand victims a year, many of them young children.

For some patients with chronic forms of the disease, treatments with X rays or radium seemed to help a little bit; at least, after such treatments, they lived perhaps a longer, and certainly a more comfortable, active life.

"Maybe radioactive sodium might be better," John Lawrence thought. "We could put it into the body easily—just feed it in a glass of water. Then it will get into the blood, spread all over, and make every blood vessel a source of rays."

Chances were that it wouldn't be dangerous. Radioactive sodium breaks down quickly, giving up most of its energy in twenty-four hours.

Lawrence and his friend Joseph G. Hamilton had already tried radioactive sodium on laboratory animals, on themselves, and on other men around the laboratory. Those early experiments, however, had been "tracer tests," aimed at seeing how fast radioactive sodium moves through the body, and only small doses of the radioactive substance had been used. Now they were ready to try large doses, doses big enough to treat disease.

In 1936, Lawrence, Hamilton, and Dr. Robert Stone gave the

first treatments of radioactive sodium to two young men who were suffering from chronic leukemia. Then, every day, they drew blood samples from these patients and made white blood cell counts. Within a week, it was obvious that the treatment was not going to be any sensational success.

"The count just wouldn't come down," the doctors reported, "and there wasn't much improvement in their symptoms. The men were still sick."

Soon they were both dead.

Then the Californians picked up another clue. The cyclotron was now producing considerable quantities of radioactive phosphorus, and for a time the scientists half-whispered to themselves that maybe they had something for cancer.

"Cancer cells grow faster than normal cells," they reasoned. "The faster a cell grows, the more phosphorus it takes up. Now, if you give radioactive phosphorus to an animal with cancer, most of the stuff ought to go to the tumor cells, and then it will give off its energy, kill the cancer, and . . ."

But it didn't work that way. True, cancer cells did take up more phosphorus than did normal cells—but only a very little bit more—and most of the phosphorus proceeded to go where phosphorus always goes, to the bones.

"Give a patient enough radioactive phosphorus to kill an internal cancer," concluded one scientist, "and you'll destroy his entire skeleton. The stuff is no good."

"Wait a moment," said Lawrence. "In leukemia the trouble is in the bone marrow. The bone marrow is working too fast, turning out too many white blood cells. And it's in the bone marrow—or anyhow in the bones—where radioactive phosphorus is deposited. Maybe we've got something!"

After preliminary tests in animals, the California group started on human beings in December, 1936, by late 1938 completed the basic studies, and then began on human patients. One of the first was a fifty-eight-year-old woman who was close to death from chronic leukemia. During the past four years, she had been given

six courses of treatment with X rays, but now the X rays were less effective, and her white count was shooting up. Within a few days after she took her first dose of radioactive phosphorus, her blood count started to drop back to normal.

Crowed the doctors: "This is what we've been looking for!"

In February, the white count went up again. Another dose of radioactive phosphorus brought it down. The same thing happened again in May, in September, and in November. Each time, an additional shot of the radioactive chemical brought the count down. Finally, after seven years she died; in her case, however, the doctors felt that radioactive phosphorus had postponed her death and moreover had given her many added months of reasonably good health.

Even more remarkable was the second patient, a twenty-nine-year-old graduate student who was brought in dying from chronic leukemia. "His count was up to a hundred and fifty-five thousand," said Lawrence. "He was a very sick man."

Within a week, after two doses of radioactive phosphorus, his symptoms were gone and his count was down to forty thousand. After three more doses, it had been pushed to the normal level of twelve thousand.

"We kept him going for years," the scientists reported afterward. "Every once in a while, we gave him another shot of radioactive phosphorus and it always seemed to work."

The patient remained alive and, of perhaps equal importance, he remained well, comfortable, happy, and useful until his death nine years later.

After years of cautious experimenting, improving their own methods and studying the results obtained by other workers, Lawrence and Hamilton and their colleagues reported that the value of radioactive phosphorus in chronic leukemia could no longer be questioned. The results on some seven hundred patients —more than four hundred of them treated by the Californians themselves—were eloquent.

"Radioactive phosphorus," they said, "is not a cure. It has not

saved the life of a single victim of chronic leukemia. Nevertheless, it appears to be at least as effective as radium or X rays and perhaps somewhat better. It postpones death, keeps the victim alive and comfortable as long as possible, lets him go about his business until nearly the very end. It appears to be relatively easy to administer, producing no irritation or unpleasantness of any kind."

Back in 1939, the Californians also considered a related ailment, equally deadly but more rare. Where chronic leukemia is marked by too many white blood cells, this disease—polycythemia vera—is marked by too many red blood cells.

"The trouble in polycythemia is also in the bone marrow," the doctors said. "Maybe radioactive phosphorus will work on this, too."

It did—and even more brilliantly than on leukemia. Two doses apiece took care of the first two patients, both middle-aged women. Their red blood cell counts plummeted to normal, their terrible headaches vanished, and they went back to normal lives. Furthermore, radioactive phosphorus not merely prolonged their lives; it apparently controlled the disease.

"Occasionally," one of the experts said, "the red count goes up again and we give some more radioactive phosphorus to knock it down again. But this can go on indefinitely. We can now hope that victims of this disease will never die from it. . . ."

At the outset, largely because they were working next door to Ernest Lawrence's cyclotron, the University of California doctors led the way in finding uses for radioactive chemicals. Their progress reports, however, were presented promptly at scientific meetings or published in scientific journals, and other scientists were quick to follow their leads. Some of these workers tried to develop new methods for the treatment of disease. Others, embarking on long-range problems, used the new radioactive chemicals to study the fundamental nature of bodily components and reactions.

"With these 'tagged' atoms," one of them explained, "we have a wonderful new tool for our studies. We can now trace any kind of

atom into the body and out of it. It is as if we could literally see the atoms."

In scores of laboratories, research men proceeded to apply these substances in hundreds of different experiments, giving them by mouth or by injection to animals and then using Geiger counters or other delicate ray-detecting machines to trace the substances from one part of the body to another. They worked out new methods to study heart disease and the action of digitalis and other heart remedies; they developed practical procedures to investigate the condition of invisible blood vessels, and applied these procedures to determine when and where an amputation was necessary in victims of frostbite, trench foot, immersion foot, hardening of the arteries, and gangrene; and they perfected ingenious methods to protect bottles of whole blood from destruction on the way from blood-donor center to battlefield. In still other laboratories, they harnessed the radioactive atoms for use in studying diabetes, epilepsy, anemia, bone and tooth formation, the chemical reaction of muscles, infections, and digestion.

"It is in this field—in solving the fundamental problems of health and disease—that the radioactive chemicals will be of the greatest benefit to mankind," declared John Lawrence. "Once we have this fundamental knowledge, then we can proceed intelligently to develop new methods of prevention and treatment. . . ."

One of the earliest examples of this sequence—first the knowledge, then the cure—came from Harvard University and the Massachusetts Institute of Technology. In 1936, Karl T. Compton, the distinguished physicist and president of MIT, was invited to describe some of the future wonders of science to the doctors and students at the Harvard Medical School. After he mentioned X rays, artificial fever, measurements of brain waves, lie detectors, and other startling phenomena, he turned to the cyclotron and the new artificial radioactive elements.

"If one of these new radioactive elements, such as sodium, is injected into the blood stream," he said, "it is possible to measure very accurately just how long it takes the blood to go from that

point to any other point in the body. . . . Similarly, radioactive phosphorus may be taken in the diet and tests made to see how rapidly this appears in the teeth. . . . An interesting possibility for treatment might be considered. Suppose, for example, a patient has cancer of the thyroid gland. If he is fed radioactive iodine, this in a short time will be concentrated right in the thyroid gland, where the radioactive radiation will be given off for a period of a few hours. . . ."

Down in the audience, a tense, soft-spoken young Harvard physician, Dr. Saul Hertz, listened to this idea and immediately got a better one. Cancer of the thyroid? That's too rare to worry about. But what about toxic goiter? What about the hundreds of thousands of victims of this disease, whose thyroid glands are working overtime, whose bodies are burning themselves out, whose hearts are weakened? Most of them can be saved by surgery, by cutting out part of that overactive thyroid, but some are already so far gone that surgery is impossible. *Would radioactive iodine serve as a substitute for surgery, melting away the tissues that should be removed?* Some doctors, he knew, had tried to do such a melting job with X rays and radium, but radioactive iodine might be infinitely superior. . . .

At the end of the lecture, Hertz literally raced to the platform. "Dr. Compton, has anyone actually made radioactive iodine yet?"

"No, I don't think so," answered Compton. "But it should be possible to make it."

"Well, if you can get some for me," said Hertz, "I'd certainly like to use it."

It took many months before Hertz got this radioactive iodine, months during which he chewed his fingernails and periodically sent polite reminders to Professor Compton. Finally, the wondrous chemical was prepared for him by Robley D. Evans, another MIT physicist. Lacking a cyclotron, Evans created it by the old-fashioned procedure, using alpha rays from a batch of radium which, fortunately, had just been willed to MIT by a recently deceased Boston doctor.

By the following year, physicist Evans, physician Hertz, and their team of coworkers were making considerable amounts of radioactive iodine and injecting it into dozens of rabbits. It made little difference, they found, how this iodine was put into a rabbit; whether it was given by mouth or by injection into a vein, an appreciable portion of it went straight to the thyroid gland. Its concentration in that gland was eighty times greater than the concentration in any other tissue.

"And if we give the rabbit an artificial form of overactive thyroid," they reported, "his thyroid tissues may accumulate several hundred times the normal concentration."

Here, then, was a chemical which could seek out its own target, and once it arrived there, its rays would start destroying tissue.

"This," said Evans, "looked like absolutely bloodless surgery. It was chemical surgery. A small dose of radioactive iodine would get rid of a little thyroid tissue. A large dose would wipe out a lot of it. We began to feel optimistic."

In the spring of 1941, after the animal experiments and after tests on two normal human volunteers, they started treatment on their first patient, an old woman who was seriously ill from an overactive thyroid, so ill that other doctors considered her a bad risk for surgery and refused to operate.

The result was clearly a flop. Probably the dosage was too small, for only a little of her thyroid was melted away and most of her unpleasant symptoms remained. The outcome was no better in the next four patients, all of them adults. In the next group of five patients, however, things went distinctly better, and clear-cut successes were marked up for four of them, including two nine-year-old children.

"Now," rejoiced some of the doctors, "we've got this thing licked."

But these overactive glands were not that easy to control. While one patient behaved the way the doctors thought he should—his thyroid gland would shrink, his bodily processes would slow down, his heart would stop its frantic fluttering, and his protruding eye-

balls would come back where they belonged—another patient would get little or no benefit at all.

All through 1942 and into 1943, Dr. Hertz treated his patients, using the radioactive iodine made for him at MIT and later supplies sent from the cyclotron in California. In the spring of that last year, after reporting his preliminary results on about twenty patients, he left Harvard to become a Navy doctor. Before he left, he asked another Harvard doctor, Earle Chapman, to carry on the work.

Chapman, who had been following the thyroid work since its beginning, inherited a not altogether satisfactory experiment. Many doctors were openly asserting that the radioactive iodine treatment was no good.

"The only treatment is surgery," one of them said. "If that can't be done, then put the patient under some X rays but don't expect too much. Radioactive iodine? Good heavens, no!"

Some physicians criticized the methods which Hertz had used, claiming that his results could not give a definite yes-or-no answer. One surgeon spoke for many of his colleagues when he claimed in a New York medical meeting that "this proposed new treatment is merely a frill, a passing fancy, dependent on some strange chemical trickling out of a strange machine called a cyclotron."

Grimly, Chapman went into his wards and began treating his own carefully selected patients. He waved away suggestions from some of his colleagues— "Better use vitamins at the same time, old boy!" "Don't you think you ought to give them some ordinary iodine, too?"—and used nothing but radioactive iodine.

"Unless we use radioactive iodine alone," he said, "we'll never know what it can do."

It took eighteen months before he could convince his colleagues that radioactive iodine can do plenty, not merely in an occasional patient but in one patient after another. By 1947, he could report apparent victory in fifty-eight out of sixty-five patients.

At the University of California, a group working under the direction of Hamilton and Dr. Mayo Soley, the university's expert on

thyroid disease, had already done a great deal of preliminary work on animals, starting that even before the MIT-Harvard group. Then they proceeded to extend the treatment to human beings, using some new types of radioactive iodine made especially for them by the cyclotron scientists.

At California, too, some older doctors were inclined to scoff at this new "passing fancy," but they quickly changed their minds. Soley soon reported the successful treatment of patient after patient, quickly, easily, painlessly, efficiently, and relatively inexpensively. He reported, too, some failures, but these were brilliantly outnumbered by the successes.

"It is quite probable," he concluded, "that the radioactive iodine treatment of this form of thyroid disease will not merely surpass the old X-ray treatment but may surpass even the use of surgery as the method of choice in most patients."

Ever since the creation of the first artificial radioactive elements back in the early 1930's, workers in this field had dreamed that they might stumble upon some new radioactive substance to turn against cancer. Year after year they kept looking for an element cheaper and safer than radium, an element which would destroy cancer cells without harming normal cells, a radioactive element which might deposit itself into a cancer cell just as radioactive iodine is deposited in the thyroid gland.

But none of these newly created elements appeared to have any ability to seek out a malignant tumor. "If you want to get them into a cancer," one researcher declared, "you just have to put them there."

That virtually ruled out any new treatment for most internal cancers. The treatment of superficial skin cancer, however, was something else.

At the University of California, enthusiastic Bertram V. A. Low-Beer figured he could use one of these radioactive chemicals in a brand-new treatment for these superficial cancers, a treatment which would be nearly the ultimate in simplicity. He first took

some radioactive phosphorus, made it up in the form of sodium phosphate, and dissolved it in water. Then he applied this solution to a patch of healthy skin on a human volunteer to see what it might do. What it did was destroy tissue, and the stronger the concentration of the solution and the longer it was kept in place, the more tissue it destroyed.

He repeated this experiment time after time, learning exactly how to control it. Then one of the men in the laboratory came to him.

"Have you tried it yet on any patients, on a real tumor?"

"No," answered Low-Beer. "But it should work on a skin cancer. Why do you ask?"

"Well, I was just wondering," said the other doctor. "You see, I've now found that I have a case of skin cancer in my own family. It's my father."

The following day, the father came to the hospital as patient Number One. Low-Beer examined him, then took an ordinary blotter and cut it with a pair of scissors so it was exactly the size of the tumor. He soaked this piece of blotter in the radioactive phosphorus solution, strapped it over the tumor with adhesive tape, and kept it there for forty-eight hours. When the blotter was removed, the tumor was red and irritated. In a few days, the tumor was gone. No fuss, no bother, no pain. It was no better than the results of treatment with X rays or radium, but it was astoundingly simple.

"The whole thing was so darn easy," remarked one observer, "that I was sure it couldn't possibly work."

But it did work. It worked on dozens of patients who were treated during the early years of World War II, when the only sources of radioactive phosphorus were a few cyclotrons. It worked on scores and finally on hundreds of others when the war was over and when radioactive phosphorus was pouring out of the enormous atomic piles.

To be sure, this phosphorus-on-a-blotter treatment was useful only for superficial cancers of the skin and was certainly not the long-sought cure for every cancer. But all over the world, wherever

science was pitted against cancer, it excited the imagination of research men and started them thinking about these new chemicals, about how they might be changed or incorporated into new compounds or administered by new and ingenious procedures. And perhaps some day . . .

Some day, there will be more chapters to this story of drugs. Scientists have invested six thousand years in their search for good drugs, but men still sicken and die needlessly. The scientists certainly won't stop now.

Even today, these stories of the future have begun. Somewhere is a physician, weary from years of ministering to his patients, who has found a strange clue. "It is odd that an old pet medicine of mine should have such an effect," he writes to a university scientist. "How about driving up here for the week end?"

Somewhere is a man with an idea that sounds crazy to everyone else, but— "Darn it all, there ought to be *something* that will get to those tumor cells. Maybe if I could get a nitrogen inside that phenanthrene nucleus and then couple some acetyl groups on the double bonds and then . . ."

Somewhere a dejected, tired scientist says, "Okay, I was wrong. It doesn't work. But maybe—maybe I ought to try it on monkeys instead of on guinea pigs. Monkeys are more like men."

Somewhere a young fellow is pleading into a laboratory telephone, "I know, darling, and I'm sorry about dinner. But I want to start one more batch of mice. I think I've got something . . ."

Somewhere tomorrow's triumphs are in the making, as fantastic as a fairy tale or as simple as ABC. Some day they, too, will be magic in a bottle.

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Index

Abbe, Robert, 343 f.
Abderhalden, Emil, 192
Abel, John Jacob, 83, 219-221, 234
Acetanilide, *see* Antifebrin
Acetyl-salicylic acid, *see* Aspirin
Achin War, 182 f.
Actinomycin, 297
Addison's disease, 234
Adrenalin (epinephrin), 114, 218-221
Afforty, 116 f.
Alkaloids, 34
Allen, Edgar, 238
Almquist, H. J., 210
Alpha-tocopherol, *see* Vitamin E
Alt, Conrad, 136
Alypin, 113
Amethone, 323 f.
Aminopyrine, *see* Pyramidon
Amoebic dysentery, 33, 38, 116 f., 138
Amyl nitrite, 84-88
Anderson, Hamilton H., 138
Anderson, Thomas, 120-122
Androsterone, 239
Anesthesia, dental, 109; general, 92-94, 114 f.; local, 98 f., 102-109, 112-114; spinal, 109
Anesthesin, 113
Angina pectoris, 83-88
Anselm, Eugen, 249
Antiaris tree, 81
Antibiotic, 298
Antifebrin (acetanilide), 157-159
Antimony, 137
Antipyrine, 154-156, 160
Antiseptics, 118-126, 271-273
Arens, J. F., 209
Arlt, Ferdinand Ritter von, 105
Arrow poisons, 81-83, 87
Aschheim, Selmar, 235-237
Aschheim-Zondek pregnancy test, 235-237
Ascorbic acid, *see* Vitamin C
Aseptic surgery, 126
Ash, John, 70 f.
Aspirin (acetyl-salicyclic acid), 160-163
Atabrine (quinacrine), 54-56, 58
Atoxyl, 132 f.
Atropine, 38
Auricular fibrillation, *see* Dropsy
Autumn Adonis, 83
Avertin, 180

Baeyer, Adolf von, 171
Banting, Frederick Grant, 229-234
Barbitals, 177-181, 314 f.
Barger, George, 226
Baron, Moses, 229 f.
Bayer *205* (Germanin), 140-144, 250
Becker, Otto, 105 f.
Becquerel, Henri, 331-336, 339-341, 343, 345
Behring, Emil von, 130 f.
Bell, Alexander Graham, 344
Bentley, W. H., 100
Beriberi, 183-193, 198, 207, 209
Bernard, Claude, 213
Bertheim, A., 133-135, 138
Berthold, A. A., 218
Besnier, Ernest, 340 f.
Best, Charles Herbert, 231-234
Black, Archie, 203 f.
Blacktongue, 207 f.
Bliss, Eleanor, 256 f., 259
Bordeu, Théophile de, 218
Boric acid, 125
Boulton, Matthew, 70
Braun, Heinrich, 113 f.
Brettauer, Joseph, 105 f.
Breuer, Joseph, 99-101
Bromides, 38, 167, 177, 304, 306-309, 311-313, 318 f.
Bromine, 304
Brower, Daniel, 111 f.

Brown, W. H., 138
Browning, Carl, 138
Brown-Séquard, Charles Édouard, 212-219, 307
Brucellosis, 297
Brucine, 34, 38
Brunton, Thomas Lauder, 84-86
Bryant, Joseph, 263-267
Bubonic plague, 297
Bugie, Betty, 297
Burke, W. C., Jr., 108 f.
Buss, Carl Emil, 150-152
Butenandt, Adolf, 238-240
Butyn, 113

Caffeine, 38
Cahn, Arnold, 156-158
Canadian hemp, 83
Cancer, 330 f., 342-347, 354, 358, 361-363
Carbarsone, 138
Carbolic acid, *see* Phenol
Carbon tetrachloride, 138
Carlson, Anton, 228 f.
Cartier, Jaques, 194
Caventou, Joseph Bienaimé, 33-38
Cevitamic acid, *see* Vitamin C
Chain, Ernst Boris, 279-282, 287 f.
Chapman, Earle M., 360
Chen, M. Y., 138
Chinchon, Count of, 26 f.; Countess of, 26-29, 32
Chloral, 167-170, 174, 177, 180; addiction, 170
Chloroform, 93 f., 167 f., 302
Chloroquine, 58
Christison, Robert, 110
Christmas rose, 83
Cinchona bark (Peruvian bark), 27-51, 59, 118; monopoly, 39-51; red, 33
Cinchophen, 160
Cobb, Stanley, 312 f.
Coca, 90 f., 93-98
Cocaine, 97-114; addiction, 95 f., 99 f., 110-112
Codeine, 38
Cod-liver oil, 199-202
Coghill, Robert D., 290-292
Colebrook, Leonard, 255 f.
Collip, James Bertram, 233 f.
Committee on Medical Research, 56-59, 290
Compton, Karl T., 357 f.
Coniine, 38
Cordus, Valerius, 91 f.
Corning, Leonard, 109, 111, 113 f.
Cortin, 234
Corvisart, Jean Nicolas, 75
Cramer, F. A., 3-9
Cross, Robert, 45, 49
Curie, Irène, 335, 349 f.
Curie, Marie Sklodowska, 335-341, 343, 345 f., 349 f.
Curie, Pierre, 335-343, 345 f., 350
Cushny, Arthur, 77-79
Cyclopropane, 115
Cyclotron, 351-353, 356-361

Dam, Henrik, 210
Danlos, Henri, 341 f.
Darwin, Erasmus, 69 f., 72-74
Davis, Marguerite, 197
Davy, Humphry, 93
Dawson, Martin, 290
Delphinine, 34
Diabetes, 174 f., 226-234, 357
Digitalin (digitoxin), 76
Digitalis (foxglove), 60-63, 66-68, 70-84, 87, 301, 357
Digitoxin, *see* Digitalin
Dilantin, 316-321
Dilthey, Alfred, 178-180
Divinyl oxide, 115
Dodoens, Rembertus, 61
Doisy, Edward, 210, 238
Domagk, Gerhard, 243-246, 248-252, 254
Dominici, Henri, 344 f.
Dominicis, Nicola de, 227 f.
Donath, W. F., 204, 209
Dorp, D. A. van, 209
Dover, Thomas, 1 f.
Dover's Powder, 2
Drake, Francis, 194
Dreser, Heinrich, 24 f., 161-163
Dropsy (auricular fibrillation), 60-63, 66-68, 70-83, 88
Dubos, René Jules, 290, 294-297
Duisberg, Carl, 158-160, 242 f.
Dysentery, 33, 117, 275